Tetrahedron Vol. 41, No. 24, pp. 5771 to 5778, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

DIRECTED REGIOSELECTIVE LITHIATION OF (η^6-ARENE)CHROMIUM TRICARBONYL COMPLEXES

REGIOSELECTIVE SYNTHESIS OF ANTHRAQUINONES AND CALAMENENES

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(*Received in USA 6 May* 1984)

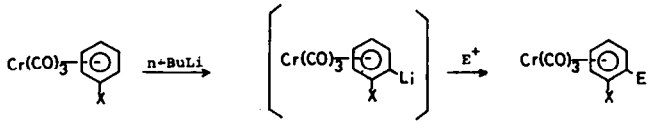
Abstract—(3-Methoxybenzylalcohol)chromium tricarbonyl (**10**) and (7-methoxy-1-tetralol)chromium tricarbonyl (**12**) are selectively lithiated at the 4- and 6-positions, respectively, by treatment with *n*-BuLi–TMEDA. Since the directed lithiation of the corresponding chromium free arenes normally proceeds at the 2- and 8-positions, complementarily substituted arenes can be prepared by using the chromium tricarbonyl complexes. The different position of lithiation is explained by the relative configuration of the chromium tricarbonyl group in the (arene)$Cr(CO)_3$ and electrostatic factors. Some anthraquinones, **31**, **36**, **42**, and 7-hydroxycalamenenes, **43**, have been synthesized through the stereo- and regioselective introduction of substituents by means of (η^6-arene)chromium tricarbonyl complexes.

Directed nuclear lithiation induced by a heteroatom substituent at its *ortho* position is an important reaction for the regioselective functionalization of aromatic compounds.[1] The groups which facilitate this *ortho* lithiation of the aromatic ring possess an electron-withdrawing effect from the aromatic nucleus and/or a co-ordinative property towards the lithium atom by a proper heteroatom in groups, such as methoxyl, methoxymethoxyl, amino, carboxamide, sulphonamide and oxazoline. This reaction provides an excellent alternative to Friedel–Crafts methodology for the synthesis of substituted arene derivatives. Recently, *ortho* lithiation of various arene compounds has been developed for natural product synthesis and reviews in this field have appeared.[2] However, the lithiation reaction sometimes requires vigorous conditions and does not give satisfactory selectivity, especially in the case of substituents with a weak *ortho* directing ability. This difficulty makes it necessary to create an activated molecule susceptible to selective lithiation.

(η^6-Arene)chromium tricarbonyl complexes, readily obtained from the arenes and chromium hexacarbonyl, are regarded as such activated molecules. They are usually air-stable, soluble in various solvents and easily handled yellow to red crystalline solids. They are usually purified by chromatography and recrystallization. (η^6-Arene)chromium tricarbonyl complexes have the following five characteristics due to the strong electron-withdrawing ability and size of the $Cr(CO)_3$ group:[3] (1) steric effect of the chromium ligand; (2) stabilization of the benzylic cation; (3) stabilization of the benzylic anion; (4) enhanced acidity of the ring hydrogens; and (5) nucleophilic addition to the arene ring. Since the arene group is readily released in a proper step from the complex by mild oxidation with aqueous Ce(IV) or iodine, or by exposure to air and sunlight, the (η^6-arene)chromium tricarbonyl complexes are useful for organic synthesis.

DIRECTED LITHIATION OF (η^6-ARENE)CHROMIUM TRICARBONYL COMPLEXES

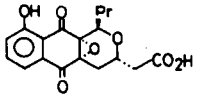
Co-ordination of the chromium tricarbonyl group to an arene enhances the kinetic acidity of the ring C—H bond. Therefore, the directed lithiation of the arene ring is expected to occur more easily than for the parent arene. It is known, however, that the reaction of (η^6-arene)$Cr(CO)_3$ with various alkyl or aryl lithium reagents can also lead to nucleophilic addition to a carbonyl (formation of a metal–carbene complex[4]) or η^6-ligand (ring alkylation[5]), depending on the reaction conditions and the nature of the bases and nucleophiles. It is, therefore, of interest to develop a more effective route to (η^6-lithioarene)$Cr(CO)_3$ in order to extend the chemistry of (arene)$Cr(CO)_3$. Generally, the reaction with *n*-BuLi at low temperature predominantly resulted in the directed lithiation of the arene ring. For example, (benzene)$Cr(CO)_3$ gives (phenyllithium)$Cr(CO)_3$ (*n*-BuLi, below −20°), which can be substituted by quenching with various electrophiles.[6] Similarly, the chromium complexes of anisole, fluoro- and chlorobenzene were lithiated in the *ortho* position to the heteroatoms (Scheme 1).[6,7]



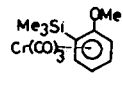
X=H, OMe, F, Cl

Scheme 1.

These results were particularly interesting, because benzene and chlorobenzene without complexation could not be easily lithiated. Since the (arene)$Cr(CO)_3$ easily undergoes regioselective nucleophilic substitution by the addition–oxidation mechanism,[8] the *ortho*-lithiation reaction, combined with *meta*-nucleophilic substitution, was ingeniously applied to the synthesis of (±)-frenolicin (**1**) from (*o*-trimethylsilylanisole)$Cr(CO)_3$ (**2**) by Semmelhack and Zask.[9]



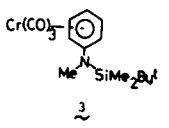
1 frenolicin



2

Proton abstraction from the (arene)$Cr(CO)_3$ occurs with different regioselectivity from that of metal-free arenes. The reaction of (*N*,*N*-dimethylaniline)$Cr(CO)_3$ with *n*-BuLi gives a regioisomeric mixture of *N*,*N*-dimethyltoluidines (*ortho*–*meta*–*para*, 31 : 50 : 19) after quenching with methyl iodide, followed by oxidation.[7c] Since *N*,*N*-dimethylaniline itself was lithiated at the *ortho* position via intramolecular co-ordination of nitrogen to the lithium atom,[10] the complexation of the chromium group clearly facilitated the *meta* substitution compared to the uncomplexed arene. In view of the fact that introduction of substituents to the *meta* position of an electron-donating group is difficult by usual aromatic substitution, it is worthwhile developing the above reaction of the chromium complexes.

Widdowson's and Oishi's groups reported independently that *meta* functionalization of the chromium tricarbonyl complexes of aniline and phenol was realized by protection of the amino or hydroxyl groups with bulky protecting groups, which sterically blocked the *ortho* position.[11] In these cases, triisopropylsilyl and *tert*-butyldimethylsilyl groups were very effective not only for blocking the *ortho* position but also for directing *meta* selectivity, as exemplified by complexes **3** and **4**. The normally dominant inductive labilization of the *ortho* proton would be effectively negated by the bulk of the protecting group. Although the origin of the *meta*-lithiation is not known with certainty, the conformation of the chromium tricarbonyl moiety to the arene ring is an important factor. X-ray crystallography of complex **3**, as well as of aniline and anisole chromium complexes,[12] has established an eclipsed structure **5**.[11b] In these complexes, *meta*-lithiation is assumed to proceed through the abstraction of a hydrogen eclipsed to the carbonyl ligand via intramolecular co-ordination of a lithium and a carbonyl oxygen atom. An extension of current theories has also suggested[13] that an electron deficiency at the eclipsed carbon atom promotes either nucleophilic attack or deprotonation, depending on the reagents employed.



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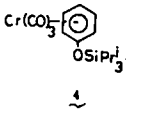

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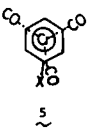

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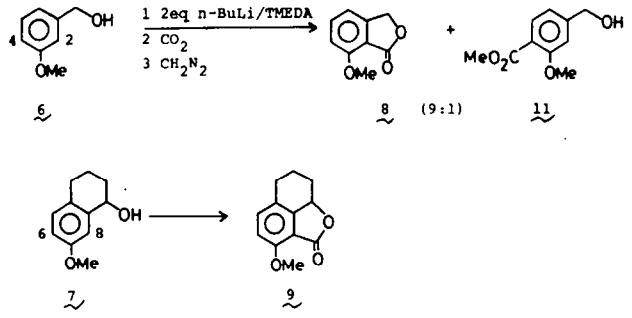
We have been interested in the regioselectivity of the nuclear lithiation in compounds where two *ortho* directing groups are located at the 1,3-position. In such compounds, lithiation occurs predominantly or exclusively at the 2-position,† even if the *ortho* directing ability of each of these substituents is not strong. For example, the lithiation of 3-methoxybenzylalcohol (**6**) and 7-methoxy-1-tetralol (**7**) occurred at the 2- or 8-position with high regioselectivity to yield γ-lactone derivatives **8** and **9** after quenching with carbon dioxide (Scheme 2).[14]

On the other hand, (3-methoxybenzylal cohol)$Cr(CO)_3$ (**10**) was found to be lithiated mainly at the 4-position. Thus, **10** was treated with 2 equivalents of *n*-BuLi and tetramethylethylenediamine (TMEDA) at −78° and then quenched with carbon dioxide to give two products (**8** and **11**) in a 23 : 77 ratio, after demetallation and subsequent methylation (Scheme 3).[15] The proportion of C-4 lithiation of complex **10** increased with increasing bulk of the alkyllithium reagent. However, chromium complex **10a** gave the 4-lithiated product exclusively, even with *n*-BuLi, presumably due to additional chelating ability of the methoxymethyl substituent. The results of (3-oxygenated benzylalcohol)chromium tricarbonyl complexes with isomeric butyllithium reagents are summarized in Table 1.

Since the effect of chromium co-ordination on the regioselectivity of aromatic lithiation was expected to be manifested more clearly by conformational fixation of the benzylic hydroxyl group, we next attempted the analogous reaction with the chromium complexes of 7-methoxy-1-tetralol and its derivatives. Indeed, *endo*-(7-methoxy-1-tetralol)$Cr(CO)_3$ (**12**) gave 7-methoxy-6-methoxycarbonyl-1-tetralol exclusively, in contrast to the result with the parent free arene mentioned above. Similarly, (2-substituted 7-methoxy-1-tetralol)$Cr(CO)_3$ afforded a single product lithiated at the 6-position in high yield (Table 2). The diastereomeric chromium complex **16** with an *exo*-hydroxyl group, still gave predominantly the 6-methoxycarbonylated product under similar reaction conditions. From the X-ray crystallography, two carbonyl ligands were found to be located in proximity to the 6- and 8-positions of the arene ring. Therefore, lithiation is presumably initiated by the formation of a lithium complex co-ordinated with both the methoxyl oxygen at C-7 and an oxygen of the carbonyl ligand, followed by abstraction of hydrogen at either the 6- or 8-position. The 8-position, however, is less susceptible to proton abstraction due to steric hindrance and electrostatic repulsion by the benzylic alkoxide anion.

Since the hydroxyalkyl group is a poor *ortho* director, lithiation of $Cr(CO)_3$ complexes possessing a benzylic ether linkage was next examined. Free arene compounds of this type, such as alkylbenzylethers and acetals of benzaldehydes, are generally not feasible for *ortho*-lithiation because of the well-known propensity for deprotonation at the benzylic position, followed by Wittig rearrangement[16] and acetal ring cleavage,[17] respectively. Reaction of (3-methoxybenzyl-

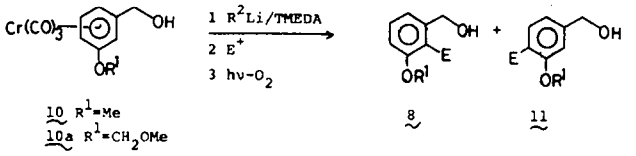
† *meta*-Oxygenated *N*-substituted benzamides, piperonal cyclohexylimine, dimethylacetal of *meta*-oxygenated benzaldehyde, oxygenated benzylamine and 2-(3-methoxyphenyl)-4,4-dimethyl-2-oxazoline are selectively lithiated at the 2-position via an intramolecular co-ordination; see Newkome.[2]



6 8 11

7 9

Scheme 2.



10 R^1=Me
10a R^1=CH_2OMe

8 11

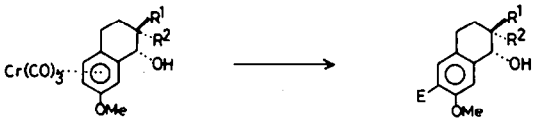
Scheme 3. Lithiation of (3-oxygenated benzyl alcohol)$Cr(CO)_3$.

Table 1

Entry	Complex	R^2	Electrophile	Ratio of 8:11	Yield (%)
1	**10**	*n*-Bu	CO_2[a]	23:77	71
2	**10**	*sec*-Bu	CO_2[a]	15:85	55
3	**10**	*t*-Bu	CO_2[a]	5:95	48
4	**10**	*t*-Bu	Me_3SiCl	6:94	50
5	**10a**	*n*-Bu	CO_2[a]	2:98	45
6	**10a**	*n*-Bu	Me_3SiCl	2:98	67

[a] Isolated as the methyl ester and γ-lactone after treatment with diazomethane.

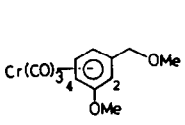
Table 2



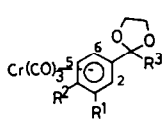
Entry	Complex	R^1	R^2	Electrophile	Yield (%)
1	**12**	H	H	CO_2	65
2	**12**	H	H	Me_3SiCl	96
3	**12**	H	H	*p*-$MeOC_6H_4CHO$	90
4	**12**	H	H	*o*-$C_6H_4(CO_2Me)_2$	91
5	**12**	H	H	MeCH=C(Me)CoCl	82
6	**13**	Me	H	CO_2	63
7	**13**	Me	H	DMF	90
8	**14**	Me	Me	DMF	92
9	**15**	CH(OH)Me	H	CO_2	55
10	**16**[a]	H	H	CO_2	52[b]

[a] *exo*-Hydroxyl complex.
[b] Ratio of products at C-6 and C-8 is 86:14.

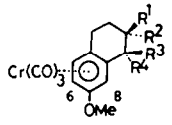
Table 3



17



18 R^1=OMe R^2=R^3=H
19 R^1=R^2=OMe R^3=H
20 R^1,R^2=OCH_2O R^3=H
21 R^1=OMe R^2=H R^3=Me



22 R^1=R^2=R^3=H R^3=OMe
23 R^1=R^2=Me R^3=H R^4=OMe

Complex	Electrophile	Lithiated positions (ratio)	Yield (%)
17	$ClCO_2Me$	2/2,4 (83:15)	67
18	$ClCO_2Me$	2/4 (93:7)	84
18	Me_3SiCl	2/2,4 (70:25)	90
19	$ClCO_2Me$	2/2,5 (80:15)	65
20	$ClCO_2Me$	2/2,5 (81:13)	92
21	$ClCO_2Me$	2/4 (51:38)	58
22	DMF	8/6 (0:100)	85
23	DMF	8/6 (0:100)	90

methylether)$Cr(CO)_3$ (**17**), however, with *n*-BuLi and, subsequently, with methylchloroformate gave 2-methoxycarbonylated and 2,4-bis-methoxycarbonylated product in an 83:15 ratio (Table 3). This result contrasts with those obtained with complex **10** which bears a free benzylic hydroxyl group. Similarly, (3-methoxybenzaldehyde ethyleneacetal)$Cr(CO)_3$ (**18**) was lithiated at the 2-position with high selectivity and the chromium complexes of other acetals also reacted predominantly at the position flanked by methoxyl and acetal groups. Since the above-mentioned electrostatic repulsion between an alkoxy anion and *n*-BuLi is absent in such cases, deprotonation at the 2-position is observed via favourable co-ordination of lithium with the proximal oxygen atoms of the two ether groups.

This chelating effect is to be distinguished from the steric effect in complex **21** in which lithiation at the 2-position is suppressed by the introduction of the methyl group at the benzylic position. The steric susceptibility of this reaction is further exemplified by tetralol methyl ether complexes **22** and **23**, which possess a conformationally fixed hindering methoxyl group at the benzylic position.† Thus, we conclude that the steric bulk of the rigid tetralin derivatives can over-ride the favourable co-ordination effect.

SYNTHESIS OF ANTHRACYCLINONE ANALOGUES

The clinical utility of the anthracycline antibiotics, daunorubicin, adriamycin and aclacinomycin A, has promoted considerable efforts to find, by partial or total synthesis, close analogues having anticancer activity and/or lower cardiotoxicity.[19] We have developed[20] regioselective synthesis of (±)-deoxyrabelomycin (**31**), (±)-decarbomethoxyaklavinone (**38**) and (±)-11-deoxydaunomycin (**42**) by applying the specific reactivity of the (arene)$Cr(CO)_3$ complexes.

Deoxyrabelomycin

The (7-methoxy-1-tetralone)$Cr(CO)_3$ was methylated with NaH and MeI to give a 2-*exo*-methyl complex which was converted into (7-methoxy-2-methyl-1-tetralol)$Cr(CO)_3$ (**24**) by stereoselective reduction.[21] Directed lithiation of the complex **24**, followed by quenching with 2-formyl-3-methoxy-*N*,*N*-diethylbenzamide and subsequent decomplexation, gave a diastereomeric mixture of hydroxyphthalide derivatives, **25**, without formation of regioisomeric products, in a 40–50% yield. Dehydration of **25** with $KHSO_4$ gave an olefinic phthalide, **26**.

The phthalide, **26**, was also obtained more easily by the following sequence. Treatment of the dilithio compound of complex **24** with DMF, followed by decomplexation and subsequent dehydration, afforded 6-formyl-7-methoxy-2-methyl-dihydronaphthalene (**27**) in a 92% yield. Condensation of **27** with the dilithio compound of 3-methoxybenzanilide gave the phthalide **26** in 80% yield.

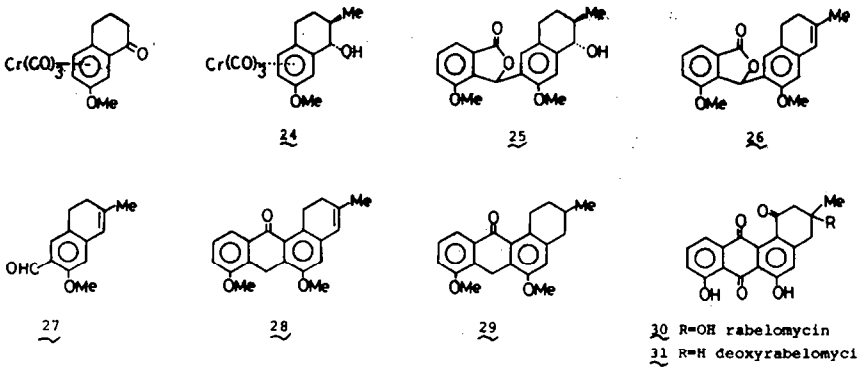
Reduction of **26** with zinc dust, followed by ring closure with trifluoroacetic anhydride and trifluoroacetic acid by the usual method, gave anthrone **28** in an 89% overall yield. Oxidation of **28** into a desired anthraquinone with retention of the olefinic double bond was troublesome.‡ However, dihydroanthrone (**29**), obtained by catalytic hydrogenation of **28**, was easily converted to an anthraquinone which gave deoxyrabelomycin (**31**)[2] by demethylation with $AlCl_3$.

Decarbomethoxyaklavinone

The anthraquinone **36**, an intermediate to decarbomethoxyaklavinone (**38**),[23] was also easily synthesized by the short, regioselective route as follows. 5-

†(*endo*-Methyl ether of 7-methoxy-1-tetralol)$Cr(CO)_3$ underwent deprotonation at the benzylic position without nuclear lithiation. The benzylic hydrogen of (arene)Cr complexes is easily abstracted by base: see Davies *et al.*[16a] and Brocard *et al.*[18].

‡Air oxidation of the anthrone **28** gave an unidentified dimeric product and an A-ring aromatized product.

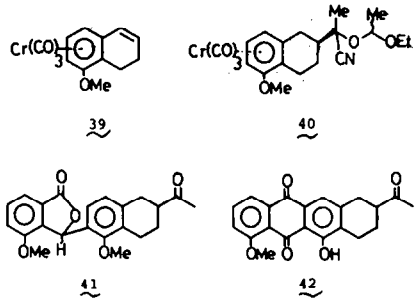


24 25 26

27 28 29 30 R=OH rabelomycin; 31 R=H deoxyrabelomycin

Methoxy-1-tetralone was converted into a (η^6-arene)$Cr(CO)_3$, **32**, in a 50% overall yield by the following sequence: (1) $Cr(CO)_6$; (2) $LiNPr^i_2$; (3) $B(OC_2H_4)_3N$, EtI; and (4) $LiAlH_4$. Treatment of the dilithio compound of complex **32** with DMF, followed by air oxidation, gave a mixture of 6- and 8-formyl compounds in a ratio of 6 : 4. This undesirable lithiation at the 8-position was attributed to the co-ordination of the lithium with the benzylic alkoxide group.[24] Exclusive introduction of the formyl group at the 6-position could be achieved by protection of the hydroxyl group as trimethylsilyl ether in an 80% overall yield. Deprotection and dehydration of **33** gave 6-formyl-5-methoxydihydronaphthalene which was converted into an anthrone, **35**, through a phthalide derivative, **34**, by the same method as described above. The anthrone, **35**, was easily oxidized (O_2, K_2CO_3) to the corresponding quinone, **36**.

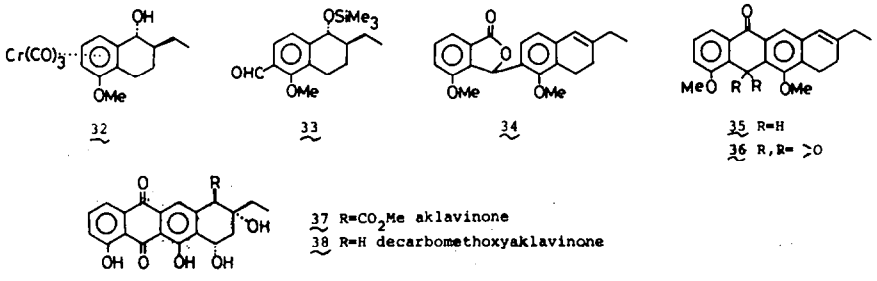
Compound **41** was converted into the anthraquinone, **42**,[28] by the procedure mentioned above.



39 40 41 42

SYNTHESIS OF 7-HYDROXYCALAMENENES

(η^6-Arene)$Cr(CO)_3$ would be applicable to the stereoselective introduction of various substituents



32 33 34 35 R=H; 36 R,R= >O

37 R=CO_2Me aklavinone; 38 R=H decarbomethoxyaklavinone

11-*Deoxydaunomycinone*[25]

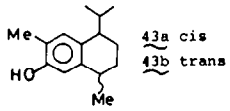
(η^6-Styrene)$Cr(CO)_3$ was recognized as the equivalent of a Michael acceptor, in which nucleophilic addition occurs at the β-position of a styrene ligand, generating the stabilized benzylic anion.[26] This nucleophilic addition to the β-position is a useful method for the synthesis of anthraquinones possessing an acyl group at C-9 since Grignard addition to β-tetralone usually proceeds giving a low yield with a large excess of the reagent because of easy enolization of the carbonyl group.[27] Thus, (5-methoxy-3,4-dihydronaphthalene)$Cr(CO)_3$ (**39**), easily obtained from 5-methoxy-1-tetralone, was converted into a (2-*exo*-substituted-5-methoxytetraline)$Cr(CO)_3$, **40**, in 87% yield by treatment with a carbanion of protected acetaldehyde cyanohydrin. Condensation of the lithio derivative of complex **40** with 2-formyl-3-methoxy-*N*,*N*-diethylbenzamide gave a diastereomeric ketophthalide derivative, **41**, by the usual method. into an alicyclic ring adjacent to the arene ring. Since co-ordination by the $Cr(CO)_3$ group confers a third dimension on the molecular structure which has stereochemical consequence, electrophilic or nucleophilic attack at the reactive centre of an alicyclic ring *ortho* condensed to an aromatic moiety always occurs stereospecifically in an *exo* fashion. This concept has been developed with the stereoselective synthesis of *cis*- and *trans*-7-hydroxycalamenenes (**43**).[29]

Reaction of methyl - 4 - (*p* - methoxyphenyl - 5 - methylhexanoate with $Cr(CO)_6$ gave the yellow (η^6-arene)$Cr(CO)_3$, **44**, which was hydrolysed to afford an acid, **45**. Although reaction of complex **45** with polyphosphoric acid was not successful, cyclization of the corresponding acid chloride with $AlCl_3$ afforded an *exo*-isopropyl tetralone complex, **46**, in a 60.5% yield, along with a trace of the *endo*-isopropyl isomer, **47**. Methyl signals of the isopropyl moiety of the major, less polar compound **46** appeared at higher field than the

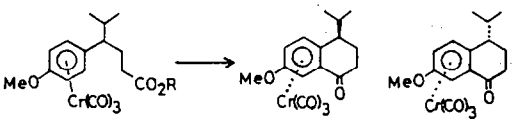
corresponding signals of the minor, more polar product **47**.[30]

Reaction of the *exo*-isopropyl complex **46** with MeLi gave a single *exo*-methylated product, **48**, which was converted to the 6-formyl complex **49** by treatment with *n*-BuLi and, subsequently, with DMF. Ionic hydrogenolysis[31] of complex **49** with an excess of Et_3SiH and CF_3CO_2H resulted in stereoselective hydride displacement at the benzylic position via a carbocation, along with the exhaustive reduction of the formyl group, giving a complex **50**. Decomplexation and subsequent demethylation gave *trans*-7-hydroxycalamenene (**43b**).

On the other hand, *endo*-isopropyl tetralone complex **47** was converted into *cis*-7-hydroxycalamenene (**43a**) through an *endo*-isopropyl–*endo*-methyl complex (**51**) by a similar reaction sequence. *cis*-7-Hydroxycalamenene was also prepared stereoselectively from complex **49** by the following procedure. Decomplexation and dehydration of complex **49** gave a dihydronaphthalene derivative, **52**, which was converted to **43a** by catalytic reduction with 10% Pd–C and subsequent demethylation.

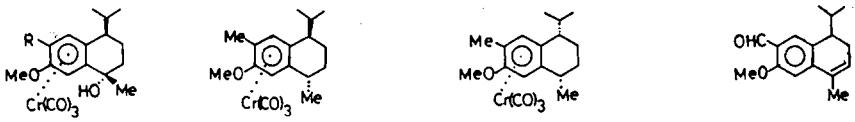


43a cis
43b trans



44 R=Me
45 R=H

46 47



48 R=H
49 R=CHO

50 51 52

EXPERIMENTAL

All m.ps are uncorrected and were determined on a Yanagimoto model MPJ-2 micro m.p. apparatus. IR spectra were recorded by a JASCO model A-102 spectrometer and ^{1}H-NMR spectra were measured on a JEOL model PS-100. NMR chemical shifts are given in ppm (δ-values) downfield from Me_4Si and coupling constants are given in Hz. Mass spectra were determined on a JEOL D-300 in the EI mode (30 eV). Elemental analysis was performed on a Perkin–Elmer model 240 automatic element analyser. Et_2O and THF were dried by distillation from sodium benzophenone ketyl before use. TMEDA was purified by distillation from CaH_2. CH_2Cl_2 was distilled from P_2O_5.

(3 - *Methoxybenzylalcohol)chromium tricarbonyl* (**10**). A mixture of 3-methoxybenzylalcohol (2.82 g, 20 mmol) and $Cr(CO)_6$ (3.3 g, 15 mmol) in heptane (75 ml) and butyl ether (150 ml) was refluxed under N_2 for 30 hr in a Strohmeier-type apparatus.[32] After filtration and evaporation *in vacuo*, a crude product was purified by SiO_2 chromatography with Et_2O–petroleum ether (1 : 4). Crystallization from Et_2O–pentane gave **10** as yellow crystals: 3.2 g (78%); m.p. 109–110°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1960, 1900–1860, 1520, 1275; ^{1}H-NMR($CDCl_3$): δ 2.12 (1H, t, J = 6 Hz), 3.57 (3H, s), 4.57 (2H, d, J = 6 Hz), 4.93 (1H, dd, J = 1 6 Hz), 5.11 (1H, d, J = 6 Hz), 5.23 (1H, d, J = 1 Hz), 5.59 (1H, d, J = 6 Hz). (Found: C, 48.20; H, 3.73. Calc for $C_{11}H_{10}O_5Cr$: C, 48.19; H, 3.68%.)

Complexes **10a**, **18**–**21**, **44** and (methoxytetralone)$Cr(CO)_3$ were obtained by a similar method. Yields and physical data are given below.

[3 - (*Methoxymethoxy)benzylalcohol]chromium tricarbonyl* (**10a**). Yield 65%; unstable yellow liquid; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1990, 1910, 1900; ^{1}H-NMR($CDCl_3$): δ 2.20 (1H, t, J = 7 Hz), 3.40 (3H, s), 4.26 (2H, d, J = 7 Hz), 4.89 (1H dd, J = 1, 6 Hz), 5.00 (2H, s), 5.20 (1H, dd, J = 1, 6 Hz), 5.30 (1H, d, J = 1 Hz), 5.50 (1H, t, J = 6 Hz).

7 - *Methoxy* - 1 - *tetralol)chromium tricarbonyl*. Yield 65%; m.p. 95–96°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1975, 1920–1880, 1685, 1540; ^{1}H-NMR ($CDCl_3$): δ 1.85–3.00 (6H, m), 3.66 (3H, s), 5.36 (1H, d, J = 6 Hz), 5.49 (1H, dd, J = 2, 6 Hz), 5.66 (1H, d, J = 2 Hz). (Found: C, 53.61; H, 3.89. Calc for $C_{14}H_{12}O_5Cr$: C, 53.85; H, 3.87%.)

(5 - *Methoxy* - 1 - *tetralone)chromium tricarbonyl*. Yield 75%; m.p. 114–115°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1990, 1920, 1910, 1650, 1510; ^{1}H-NMR($CDCl_3$): δ 1.85–3.28 (6H, m), 3.72 (3H, s), 5.26 (1H, d, J = 6 Hz), 5.43 (1H, t, J = 6 Hz), 5.70 (1H, d, J = 6 Hz). (Found: C, 53.81; H, 3.93. Calc for $C_{14}H_{12}O_5Cr$: C, 53.85; H, 3.87%.)

(3 - *Methoxybenzaldehyde ethyleneacetal)chromium tricarbonyl* (**18**). Yield 92%; m.p. 105°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1980, 1900 (br), 1540; ^{1}H-NMR($CDCl_3$): δ 3.78 (3H, s), 4.12 (4H, m), 5.04 (1H, d, J = 6 Hz), 5.14 (1H, dd, J = 2, 6 Hz), 5.38 (1H, d, J = 2 Hz), 5.56 (1H, t, J = 6 Hz), 5.64 (1H, s). (Found: C, 49.31; H, 3.85. Calc for $C_{13}H_{12}O_6Cr$: C, 49.38; H, 3.83%.)

(3,4 - *Dimethoxybenzaldehyde ethyleneacetal)chromium tricarbonyl* (**19**). Yield 75%; m.p. 125–126°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1980, 1910, 1890; ^{1}H-NMR($CDCl_3$): δ 3.78 (3H, s), 3.82 (3H, s), 4.08 (4H, m), 5.24 (2H, s), 5.50 (2H, s). (Found: C, 48.56; H, 4.07. Calc for $C_{14}H_{14}O_7Cr$: C, 48.54; H, 4.08%.)

(*Piperonalethyleneacetal)chromium tricarbonyl* (**20**). Yield 37%; m.p. 99–101°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1975, 1890 (br), 1460, 1260; ^{1}H-NMR($CDCl_3$): δ 4.06–4.14 (4H, m), 5.19 (1H, d, J = 7 Hz), 5.45 (1H, d, J = 7 Hz), 5.51 (1H, s), 5.70 (2H, s), 5.96 (1H, s). (Found: C, 47.29; H, 3.05. Calc for $C_{13}H_{10}O_7Cr$: C, 47.28; H, 3.05%.)

(3 - *Methoxyacetophenone ethyleneacetal)chromium tricarbonyl* (**21**). Yield 92%; m.p. 92–93°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1980, 1900–1890, 1050; ^{1}H-NMR($CDCl_3$): δ 1.72 (3H, s), 3.77 (3H, s), 4.10–4.25 (4H, m), 5.17–5.24 (2H, m), 5.43–5.48 (2H, m). (Found: C, 50.80; H, 4.31. Calc for $C_{14}H_{14}O_6Cr$: C, 50.92; H, 4.27%.)

[*Methyl* - 4 - (*p* - *methoxyphenyl*) - 5 - *methylhexanoate]chromium tricarbonyl* (**44**). Yield 78%; m.p. 53–54°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1970, 1880, 1740; ^{1}H-NMR($CDCl_3$): δ 0.85 (6H, t, J = 6 Hz), 1.70–2.60 (6H, m), 3.72 (3H, s), 3.76 (3H, s), 5.10 (2H, m), 5.44 (2H, m). (Found: C, 56.19; H, 5.74. Calc for $C_{18}H_{22}O_6Cr$: C, 55.96; H, 5.74%.)

(3 - *Methoxybenzylmethylether)chromium tricarbonyl* (**17**). A mixture of **10** (474 mg, 1.7 mmol) in dry Et_2O (10 ml) was added by a syringe into a mixture of NaH (50% oil dispersion, 110 mg,

2.29 mmol) in Et_2O (10 ml) and DMF (5 ml) at 0° under N_2. After 30 min, 0.5 ml of MeI was added and the mixture was stirred for 3 hr. After addition of H_2O, the mixture was extracted with Et_2O. The extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by SiO_2 chromatography (Et_2O–petroleum ether) to give complex **17** as yellow crystals: 479 mg; m.p. 59°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1960, 1900–1860, 1460, 1280; ^{1}H-NMR($CDCl_3$): δ 3.48 (3H, s), 3.74 (3H, s), 4.10 (2H, s), 4.70 (1H, d, J = 6 Hz), 4.90 (1H, d, J = 6 Hz), 5.08 (1H, s), 5.46 (1H, t, J = 6 Hz). (Found: C, 48.20; H, 3.73. Calc for $C_{12}H_{12}O_5Cr$: C, 48.19; H, 3.68%.)

endo - (7 - Methoxy - 1 - tetralol)chromium tricarbonyl (**12**). A soln of the Cr complex of 7-methoxy-1-tetralone (1.0 g, 3.2 mmol) in dry Et_2O (30 ml) was added to a mixture of $LiAlH_4$ (487 mg, 12.8 mmol) in Et_2O (20 ml) at 0° under N_2. After stirring for 3 hr H_2O was added. After filtration and evaporation of the organic solvent under reduced pressure, the residue was purified by SiO_2 chromatography to give complex **12** (800 mg) as yellow crystals: m.p. 121°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1960, 1880–1860; ^{1}H-NMR($CDCl_3$): δ 3.89 (3H, s), 4.66–4.98 (1H, m), 5.47 (1H, dd, J = 2, 7 Hz), 5.63 (1H, d, J = 7 Hz), 5.70 (1H, d, J = 2 Hz). (Found: C, 53.38; H, 4.69. Calc for $C_{14}H_{14}O_5Cr$: C, 53.51; H, 4.49%.)

exo - (7 - Methoxy - 1 - tetralol)chromium tricarbonyl (**16**). A soln of the *endo*-complex **12** (980 mg, 3.1 mmol) in CH_2Cl_2 (4 ml) was added to a mixture of conc H_2SO_4 (7 ml) and CH_2Cl_2 (7 ml) at −15° under Ar. After stirring for 2 min, the mixture was decomposed with ice–H_2O and worked-up as usual. Chromatography with SiO_2 gave the pure *exo*-complex **16** (490 mg): m.p. 90–92°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1960, 1885–1860; ^{1}H-NMR($CDCl_3$): δ 3.72 (3H, s), 4.77 (1H, t, J = 6 Hz), 5.19 (1H, dd, J = 2, 7 Hz), 5.39 (1H, d, J = 2 Hz), 5.47 (1H, d, J = 7 Hz). (Found: C, 53.22; H, 4.67. Calc for $C_{14}H_{14}O_5Cr$: C, 53.51; H, 4.49%.)

exo - (1,7 - Dimethoxytetraline)chromium tricarbonyl (**22**). Conc H_2SO_4 (10 ml) was added slowly to a soln of the *endo*-complex **12** (1.0 g, 3.18 mmol) in MeOH (20 ml) at −10° under Ar. The mixture was stirred for 10 min and poured into ice–H_2O and worked-up as usual. Purification by SiO_2 chromatography (Et_2O–petroleum ether) gave complex **22** (520 mg): m.p. 72°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1980, 1900, 1890, 1550; ^{1}H-NMR($CDCl_3$): δ 3.54 (3H, s), 3.74 (3H, s), 4.32 (1H, t, J = 6 Hz), 5.20 (1H, dd, J = 2, 6 Hz), 5.32 (1H, d, J = 2 Hz), 5.46 (1H, d, J = 6 Hz). (Found: C, 55.00; H, 4.90. Calc for $C_{15}H_{16}O_5Cr$: C, 54.88; H, 4.91%.)

General procedure for the lithiation of Cr complexes. Unless otherwise specified, all reactions were performed in flame-dried glassware under Ar by dropwise addition of a soln of the complex in dry THF or Et_2O to a soln of a 1:1 alkyllithium–TMEDA complex in dry THF or Et_2O at −78°. After the reaction period, the mixture was treated with an electrophile at −78°. After allowing the mixture to warm to ambient temp H_2O was added and the mixture was then extracted with Et_2O. The extract was exposed to sunlight for several hours until the colour of the complex disappeared. After filtration and washing of the filtrate with brine, removal of the solvent *in vacuo* gave the crude product, which was purified by chromatography. The ratio of the products was determined by ^{1}H-NMR spectroscopy and GLC. A typical example follows.

Methoxycarbonylation of complex **6**. To a soln of **6** (274 mg, 1 mmol) and TMEDA (278 mg, 2.4 mmol) in dry Et_2O (15 ml) at −78° was added dropwise 1.6 ml of *n*-BuLi (1.5 M in hexane, 2.4 mmol) under Ar. After stirring for 4 hr, the resulting mixture was poured into dry-ice in Et_2O. After being allowed to stand overnight, the mixture was acidified with dil HCl and the product was then extracted with Et_2O. The extract was exposed to sunlight for 2 hr to give a colourless soln. The ppt was filtered off and the soln was then treated with an excess of diazomethane. After evaporation of the solvent under reduced pressure, the ratio of the crude product was determined by GLC (3% OV-1, 1.5 m, 150°) and ^{1}H-NMR. Purification by SiO_2 chromatography gave two carboxylated products. 7-Methoxyphthalide (**8**): 26 mg; m.p. 110° (lit.[33] m.p. 107–109°); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745; ^{1}H-NMR($CDCl_3$): δ 3.90 (3H, s), 5.17 (2H, s), 6.83 (1H, dd, J = 2, 8 Hz), 6.93 (1H, dd, J = 2, 8 Hz), 7.50 (1H, t, J = 8 Hz). (Found: C, 65.81; H, 4.90. Calc for $C_9H_8O_3$: C, 65.83; H, 4.91%.)

Compound **11**: 145 mg; colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1710, 1610; ^{1}H-NMR($CDCl_3$): δ 3.86 (6H, s), 4.70 (2H, s), 6.89 (1H, dd, J = 1, 8 Hz), 6.97 (1H, d, J = 1 Hz), 7.73 (1H, d, J = 8 Hz). MS: *m/z* (%) 196 $[M]^+$ (46), 165 (100), 163 (82).

Preparation of methoxyphthalide **26**. Complex **24** (328 mg, 1 mmol) was lithiated with *n*-BuLi (2.5 mmol) and TMEDA (2.5 mmol) in dry Et_2O (20 ml) by a similar method to that described above. A soln of 2-formyl-3-methoxy-*N*,*N*-diethylbenzamide (350 mg, 1.5 mmol) in dry Et_2O (20 ml) was added into the lithiated mixture at −78°. After work-up as usual, crude hydroxyphthalide, **25**, was obtained (220 mg). A mixture of **25** and $KHSO_4$ (200 mg) was heated at 180° for 10 min under N_2. After cooling to room temp and the addition of H_2O, the mixture was extracted with CH_2Cl_2 and worked-up as usual. Purification by SiO_2 chromatography gave **26** (180 mg); m.p. 173–174°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1610, 1490, 1280, 1100; ^{1}H-NMR($CDCl_3$): δ 1.92 (3H, s), 2.18 (2H, t, J = 8 Hz), 2.62 (2H, t, J = 8 Hz), 3.72 (3H, s), 3.80 (3H, s), 6.14 (1H, br, s), 6.44 (1H, s), 6.52 (1H, s), 6.72 (1H, s), 6.90–7.18 (1H, m), 7.40–7.54 (2H, m). MS: *m/z* (%) 334 $[M-H_2]^+$ (100), 303 (31), 275 (20). (Found: C, 74.79; H, 5.88. Calc for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99%.)

Preparation of anthrone **28**. A suspension of **26** (282 mg, 0.84 mmol), Zn dust (5.39 g), $CuSO_4 \cdot 5H_2O$ (0.16 g) and pyridine (1.1 ml) in 10% KOH aq (27 ml) was stirred vigorously at 90° for 2 days. After filtration, the eq soln was acidified to pH 1 with conc HCl and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give an acid (300 mg) as crystals. To a cold soln (−15°) of the acid (300 mg) in dry CH_2Cl_2 were added sequentially trifluoroacetic anhydride (0.38 ml) and trifluoroacetic acid (0.38 ml) at −15°. The pale brown soln was stirred for 1 hr at −15°, for 30 min at 0° and for 2 hr at room temp and then poured into cold sat $NaHCO_3$ aq. The mixture was extracted with CH_2Cl_2 and the extract was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by SiO_2 chromatography to give **28** (238 mg, 89%): m.p. 196°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650, 1600, 1460; ^{1}H-NMR($CDCl_3$): δ 1.94 (3H, s), 2.22 (2H, t, J = 8 Hz), 3.48 (2H, t, J = 8 Hz), 3.86 (3H, s), 3.88 (3H, s), 3.98 (2H, s), 6.14 (1H, br, s), 6.68 (1H, s), 6.96 (1H, d, J = 8 Hz), 7.28 (1H, t, J = 8 Hz). MS: *m/z* (%) 320 $[M]^+$ (20), 318 (100), 317 (67). (Found: C, 78.75; H, 6.28. Calc for $C_{21}H_{20}O_3$: C, 78.72; H, 6.29%.)

Hydrogenation of **28**. A mixture of **28** (150 mg, 0.47 mmol) and a catalytic amount of 10% Pd–C in EtOAc (60 ml) was stirred at room temp under H_2 (1 atm) for 4 hr. After filtration, the soln was concentrated to give **29** (150 mg): m.p. 187°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660, 1600, 1460; ^{1}H-NMR($CDCl_3$): δ 1.06 (3H, d, J = 6 Hz), 1.18–3.52 (7H, m), 3.88 (3H, s), 3.93 (3H, s), 3.97 (2H, s), 6.72 (1H, s), 6.98 (1H, d, J = 8 Hz), 7.32 (1H, t, J = 8 Hz), 7.80 (1H, d, J = 8 Hz). (Found: C, 78.23; H, 6.89. Calc for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88%.)

Dimethoxydeoxyrabelomycin. CrO_3 (100 mg, 1 mmol) was added to a soln of **29** (100 mg, 0.3 mmol) in HOAc (40 ml) and the resulting mixture was stirred at 25° for 4 hr and then concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and Na_2CO_3 aq and the aq phase was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography to give dimethoxyrabelomycin (90 mg): m.p. 236–239°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1670, 1590; ^{1}H-NMR($CDCl_3$): δ 1.18 (3H, t, J = 6 Hz), 3.96 (3H, s), 3.99 (3H, s), 6.88 (1H, s), 7.14 (1H, t, J = 6 Hz), 7.58 (2H, d, J = 6 Hz). MS: *m/z* (%) 350 $[M]^+$ (72), 335 (100). (Found: C, 72.19; H, 5.08. Calc for $C_{21}H_{18}O_5$: C, 71.98; H, 5.19%.)

Cyclization of **45** *to give* **46** *and* **47**. A mixture of complex **45** (6.01 g, 16.1 mmol) and oxalyl chloride (12.0 g, 94.5 mmol) in dry C_6H_6 (500 ml) was heated at 50° for 2 hr under N_2. The solvent and excess reagent were evaporated *in vacuo* to give an

acid chloride complex as a yellow oil, which was used for the next step without purification. To a soln of the acid chloride in dry CH_2Cl_2 (400 ml) was added all at once anhyd $AlCl_3$ (25 g, 18.4 mmol) at 0°. The mixture was stirred at 0° for 30 min and then at room temp for 2 hr. After addition of H_2O the mixture was extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$ aq and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a red oil which was purified by chromatography to give two pure products. The *exo*-isopropyl complex **46** (3.45 g): m.p. 90°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1980, 1900, 1690, 1540; ^{1}H-NMR($CDCl_3$): δ1.02 (3H, d, J = 6.3 Hz), 1.08 (3H, d, J = 6.3 Hz), 1.62–3.68 (6H, m), 3.72 (3H, s), 5.44 (2H, s), 5.60 (1H, s). (Found: C, 57.76; H, 5.14. Calc for $C_{17}H_{18}O_5Cr$: C, 57.63; H, 5.12%.) The *endo*-isopropyl complex **47** (166 mg): m.p. 132–133°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1980, 1910, 1690; ^{1}H-NMR($CDCl_3$): δ 1.06 (3H, d, J = 6.3 Hz), 1.18 (3H, d, J = 6.3 Hz), 1.24–2.74 (6H, m), 3.66 (3H, s), 5.32 (1H, dd, J = 2, 5 Hz), 5.64 (1H, d, J = 2 Hz), 5.68 (1H, d, J = 5 Hz). (Found: C, 57.59; H, 5.14. Calc for $C_{17}H_{18}O_5Cr$: C, 57.63; H, 5.12%.)

Reaction of **46** *with* MeLi *to give* **48**. To a soln of **46** (3.41 g, 9.57 mmol) in dry Et_2O (200 ml) was added 7.6 ml of MeLi (11.4 mmol, 1.5 M in Et_2O) at −78° under N_2. After stirring at 0° for 1.5 hr, H_2O was added. The mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4 and evaporated. The resulting oil was purified by chromatography to give **48** (2.23 g, 63%): m.p. 122°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640, 1980, 1900, 1540; ^{1}H-NMR($CDCl_3$): δ 0.68 (3H, d, J = 7 Hz), 0.94 (3H, d, J = 7 Hz), 1.52 (3H, s), 3.68 (3H, s), 5.27 (1H, dd, J = 3, 7 Hz), 5.52 (1H, d, J = 3 Hz), 5.63 (1H, d, J = 7 Hz). (Found: C, 58.51; H, 6.00. Calc for $C_{18}H_{22}O_5Cr$: C, 58.37; H, 5.99%.)

Conversion of **48** *to give* **49**. To a mixture of **48** (1.47 g, 3.96 mmol) and TMEDA (1.44 ml, 9.5 mmol) in dry Et_2O (42 ml) was added 7.34 ml of *n*-BuLi (1.3 M in hexane, 9.5 mmol) at −78° under N_2. After the mixture had been stirred for 2.5 hr, 1.5 ml of DMF (20 mmol) was added all at once. The reaction mixture was warmed to 0° for 2 hr. After addition of H_2O, the mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4 and rotary evaporated. The crude product was purified by chromatography to give **49** (1.34 g, 85%): m.p. 142–144°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640, 1970, 1890, 1680, 1540; ^{1}H-NMR($CDCl_3$): δ 0.82 (3H, d, J = 6 Hz), 1.06 (3H, d, J = 6 Hz), 1.60 (3H, s), 3.80 (3H, s), 5.42 (1H, s), 6.39 (1H, s), 10.01 (1H, s). (Found: C, 57.46; H, 5.62. Calc for $C_{19}H_{22}O_6Cr$: C, 57.29; H, 5.57%.)

Acknowledgements—This work was supported by Grants-in-Aid for Scientific Research (Nos. 57470026, 57540310 and 58540321) and by a Special Project Research grant (No. 58210026) from the Ministry of Education, Japan.

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