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STEREO- AND REGIOSELECTIVE SYNTHESIS OF HYDROXYCALAMENENES VIA (ARENE)TRICARBONYL CHROMIUM COMPLEXES

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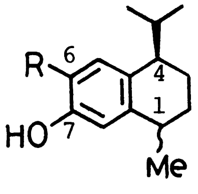
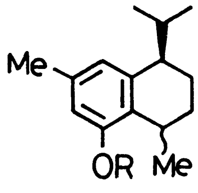
Stereoisomers of 7- and 8-hydroxycalamenenes were synthesized stereo- and regioselectively via (arene)tricarbonyl chromium complexes.

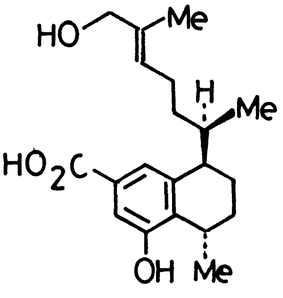
Phenolic cadinane-type sesquiterpenoids, 7-hydroxy-*cis*-calamenene (1a),[1)] 7-hydroxy-*cis*-calamenal (2a),[2)] and 8-hydroxy and methoxy-*trans*-calamenene (3b and 4b),[3)] and a prenylated analog, dihydroxyserrulatic acid (5),[4)] have been isolated from plant origin, and a remarkable fish-poison activity has been shown for the compounds 1a and 3b. For the general synthesis of these terpenoids, it is necessary to introduce the benzylic substituents stereoselectively, and the aromatic substituent regioselectively at the proper position in the terpenoid skeleton. We now wish to report the stereo- and regioselective synthesis of the hydroxycalamenenes by employing stereoselective alkylation at the benzylic position and regioselective functionalization at aromatic part of (arene)tricarbonyl chromium complexes.



1 R=Me
2 R=CHO
a, cis : b, trans



3 R=H
4 R=Me
a, cis : b, trans



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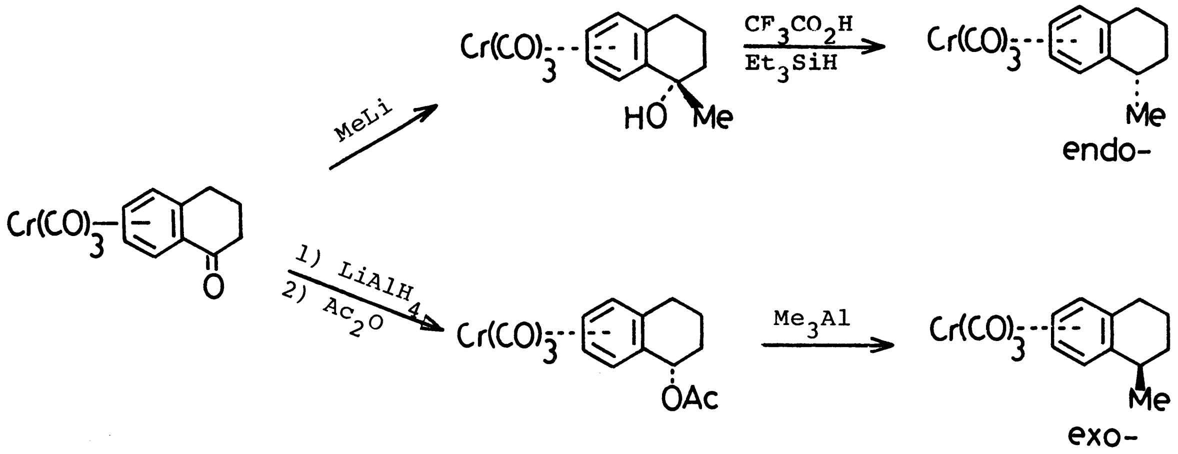
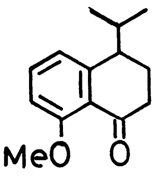
(Arene)tricarbonyl chromium complexes have some characteristic properties due to the strong electron-withdrawing ability and steric bulkiness of $Cr(CO)_3$ group. One consequence is a three dimensional structure of the planar aromatic moiety, which controls stereochemistry on nucleophilic or electrophilic attack at the reactive center of an alicyclic ring. Another one is remarkable stability of the benzylic carbocations.[5)] As a synthetic application of the above two concepts, both isomers of tricarbonyl(1-methyltetralin)chromium were selectively prepared from tricarbonyl(α-tetralone)chromium as follows (Scheme 1), giving the key reactions for the synthesis of these terpenoids.



Scheme 1.

Since attempts to the direct complexation of 4-isopropyl-8-methoxy-1-tetralone (6), obtained from m-methoxybenzaldehyde by several steps, with $Cr(CO)_6$ gave a complex mixture[6)] under various conditions, the tetralone 6 was converted into the ethylene acetal derivative 7. The acetal 7 smoothly provided the corresponding (η^6-arene)tricarbonyl chromium complex under usual thermal conditions and subsequent acid treatment gave the desired (4-*exo*-isopropyl-8-methoxy-1-tetralone)$Cr(CO)_3$ 8, (mp 102-103 °C) in 82% overall yield, along with a trace of the *endo*-isomer. This reaction proceeded selectively so that the isopropyl group at the chiral benzylic position was oriented far from the bulky $Cr(CO)_3$ group, and afforded the *exo*-isomer 8 predominantly. Reaction of the complex 8 with MeLi gave a single *exo*-methylated product 9, (mp 138 °C) in 61% yield. Ionic hydrogenolysis[7)] of the benzylic alcohol in the complex 9 with an excess of triethylsilane and trifloroacetic acid resulted in a stereoselective hydride displacement, giving the (1-*endo*-methyl-4-*exo*-isopropyl-8-methoxytetralin)$Cr(CO)_3$ (10, mp 120 °C) in 75% yield without stereoisomeric contamination. Nucleophilic addition8) of 2-lithio-1,3-dithian to the complex 10 and subsequent oxidative decomplexation of the anionic chromium intermediate with iodine gave 6-dithianylated compound 12b, (25% yield) and 6-formylated compound 13b (36% yield). *trans*-8-Methoxycalamenene (4b) was obtained from the compound 12b by desulfurization with Raney Ni, and also from 13b by hydrogenation with Pd/C, in good yields. Demethylation of the compound 4b with BBr_3 afforded *trans*-8-hydroxycalamenene (3b).

The *endo*-acetate complex 14, prepared from 8 by reduction and subsequent acetylation, was converted into (1-*exo*-methyl-4-*exo*-isopropyl-8-methoxytetralin) $Cr(CO)_3$ (11, mp 106 °C) via stereoselective *exo*-methyl displacement at the benzylic position by Me_3Al treatment9) in 99% yield. The complex 11 was converted into *cis*-8-hydroxycalamenene (3a) through 6-substituted products 12a and 13a under the same reaction sequence as described above.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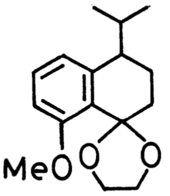
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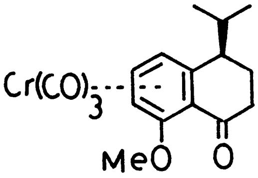
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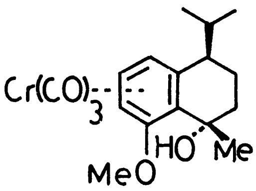
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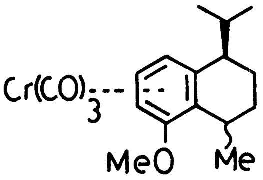
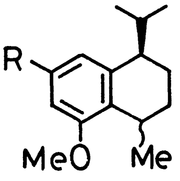
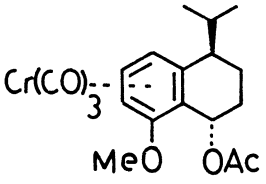

10 endo-Me
11 exo-Me


12 $R=\overline{CHS(CH_2)_3S}$
13 R=CHO
a, cis : b, trans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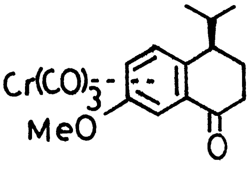
Similarly, the *cis*-7-hydroxycalamenene (1a) was synthesized as follows. (4-*exo*-Isopropyl-7-methoxy-1-tetralone)$Cr(CO)_3$ (15), major cyclization product of [4-(p-methoxyphenyl)-5-methylhexanoyl chloride]$Cr(CO)_3$ with $AlCl_3$, was converted into (1-*exo*-methyl-4-*exo*-isopropyl-7-methoxytetralin)$Cr(CO)_3$ (17, mp 125 °C) through an *endo*-acetate complex 16 (mp 155 °C) by reduction, acetylation and methylation with Me_3Al in 80% overall yield. Directed lithiation10) (BuLi, TMEDA, THF, -78 °C, 2 h) of the complex 17 and subsequent quenching with dimethylformamide gave 6-formylated complex 18 (mp 164 °C) in 83% yield without formation of regioisomeric products. Decomplexation of 18 (exposure to sunlight), hydrogenolysis with Pd/C and subsequent demethylation with BBr_3 afforded *cis*-7-hydroxycalamenene (1a) in good yield. The stereoselective synthesis of *trans*-7-hydroxycalamenene (1b) from the complex 15 was already reported.[11)]



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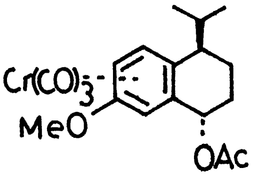

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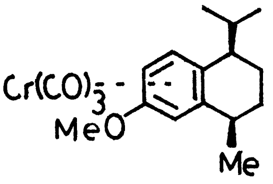

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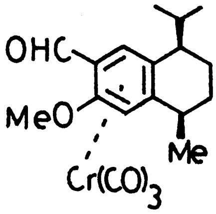

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