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A NEW ANNULATION REACTION USING THE STEREOSELECTIVE ACTIVATION OF "BENZYLIC" PROTONS IN THE $Cr(CO)_3$ COMPLEXES OF INDANONE AND TETRALONE DERIVATIVES.

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In the syntheses of natural products the methods of formation of 5 and 6-membered additional rings from a pre existing cyclic ketone have undoubtedly attracted a great deal of attention. Problems concerned *inter alia* with the processes of annulation and the stereochemistry of molecules derived from the "indanone" and "tetralone" skeletons have been discussed extensively (1, 2).

The modification of symmetry on incorporation of the $Cr(CO)_3$ moiety allowed access to optically active 1-indanone and 1-tetralone $Cr(CO)_3$ (3). Moreover, the ease of complexation and displacement of the $Cr(CO)_3$ activating group makes it a reagent of choice in synthesis. Further applications of this principle with respect to the chemistry of natural products seemed promising.

We report here our preliminary results in this specific area.

The base catalyzed Michael addition of MVK (Methyl Vinyl Ketone) to a ketone is not generally a stereoselective reaction, whatever the substrate is. Starting from either *endo* 2-methyl 1-indanone $Cr(CO)_3$ or the *exo* isomer or a mixture of these derivatives 1 in a benzene solution in presence of a weak base (DBN) (4), the vapor phase introduction of MVK (5) gave (yield 90 % ; based on isolated products) 2 (mp 95°, 13 %, $\delta_{CH_3\ exo}$ 1.23 $CDCl_3$) and 3 (mp 108°, 87 %, $\delta_{CH_3\ endo}$ 1.43)(6) in a highly stereoselective reaction.

The second step of a classical Robinson annulation occurs via an aldol condensation, but changing only the position of the substituents at C-2 in 2 and 3 results in an unexpected cyclization of the *exo* chain in 3. Base treatment (methanolic solution of Triton B, benzene, room temperature, 1 hr) of 2 gave the diastereoisomeric α-enone 4 (yield 91 %, mp 158°, $\delta_{CH_3\ exo}$ 1.33, $\delta_{CH=C}$ 6.20 $CDCl_3$). Under the same conditions, 3 underwent two competitive cyclizations : the first one led to the expected α-enone 5 (mp 225°, $\delta_{CH_3\ endo}$ 1.67, $\delta_{CH=C}$ 6.20, $CDCl_3$, yield 5-10 %) whereas the second largely predominant process (> 90 %) gave rise to the keto alcohols 6 and 7 (ratio 6/7 ≃ 45/55)(6, mp 109° ; 7 mp 170°).

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The configurational assigment of 6 and 7 by means of combined NMR-methods, will be reported later (7).

This unusual annulation provides an interesting new example of stereospecific activation of the methylene protons in α-position to the complexed ring by $Cr(CO)_3$. Similar activation was already mentioned in open chain models (8a, 8b) and in the deuteration of indan-$Cr(CO)_3$ derivatives (8a). Recently CECCON (9) found that complexation results in an activation by a factor of the order of 10^2 with respect to formation of a carbanion centre α to the ring.

The stereochemistry at the C-atom 2 and also the stereoelectronic effects of $Cr(CO)_3$ govern the course of the ring closure. In 2 the only possibility is the normal aldol condensation which affords the α-enone 4, while in 3 the *exo* face of the molecule is not hindered and an *exo* attack on the activated 3-carbon atom predominates.

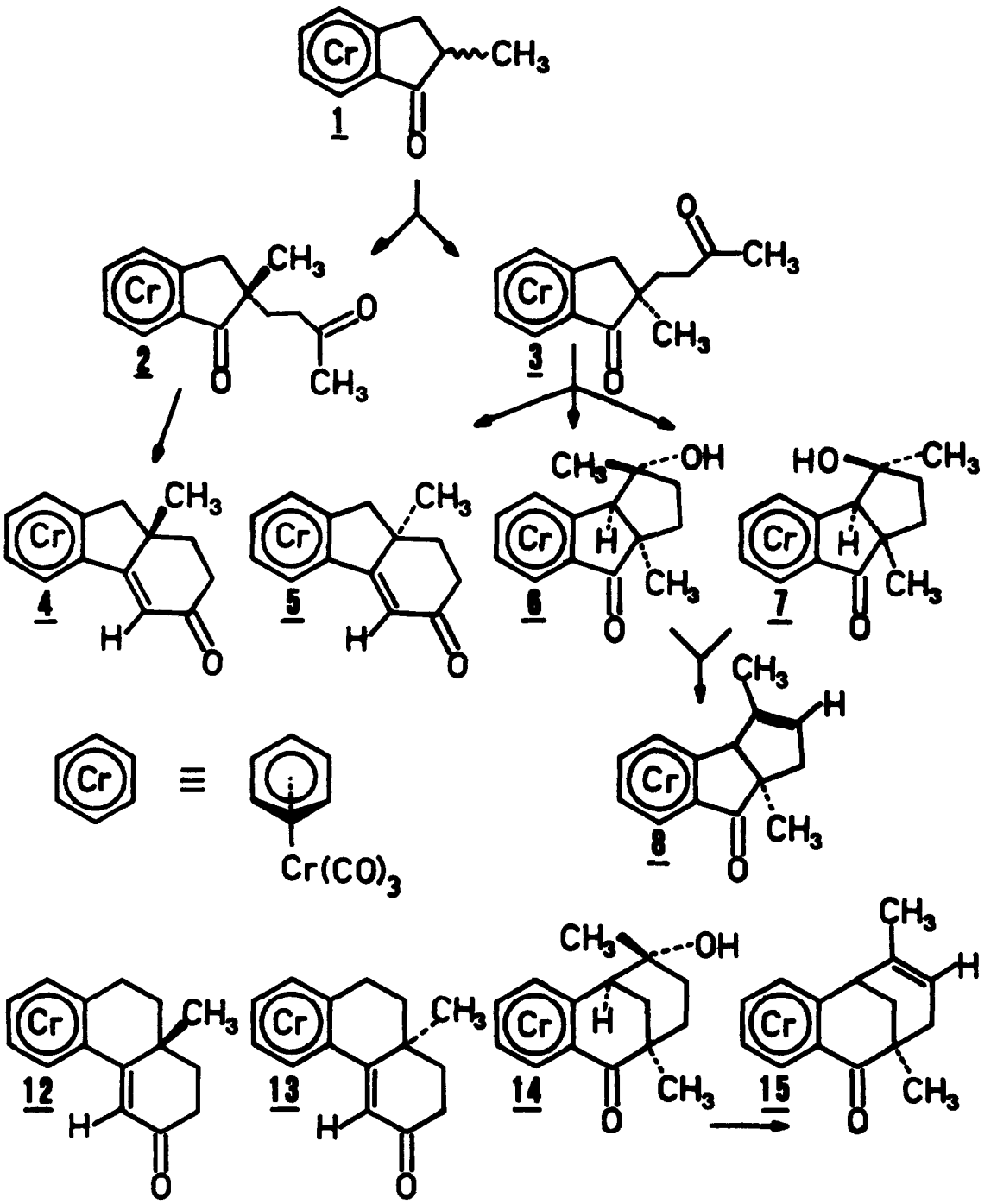
In addition, treatment of the keto alcohols 6 and 7 with $SOCl_2$ in pyridine produced the same ketone 8 (yield 90 %)(mp 190°, $\delta_{CH_3\ endo}$ 1.57, $\delta_{C(CH_3)=C}$ 1.88, $\delta_{CH=C}$ 5.30).

An identical annulation sequence has been performed with 2-methyl 1-tetralone $Cr(CO)_3$ giving rise to the two Michael adducts 10 (mp 148°, *exo* Me) and 11 (main product, mp 114°, *endo* Me)(ratio 10/11 = 1/6.5).

Treatment with Triton B converted 10 into the expected α-enone 12 corresponding to 4 (mp 166°, $\delta_{CH_3\ exo}$ 1.25). Annulation of the major product 11 gave the alternate process as well : small amounts of 13 (mp 153°, $\delta_{CH_3\ endo}$ 1.53) were observed but the remarkable cyclization yielding specifically the keto alcohol 14 (mp 141°) was largely predominant (10). The structural determination of 14 will be described in detail in the full paper (7). In this step (11 → 14) it should be noted that two reaction sites are possible, resulting in either formation of a 5- or 6-ring upon closure. Only a 6-membered ring is observed (7), therefore the attack takes place solely at the $Cr(CO)_3$-activated 4-carbon and not at the adjacent one to the keto side chain (11). The keto alcohol 14 can be easily converted by dehydration into the non conjugated enone 15 (mp 145°, $\delta_{CH_3\ endo}$ 1.30, $\delta_{C(CH_3)=C}$ 1.77, $\delta_{CH=C}$ 5.26).

Application to optically active precursors

From the (-) *exo* 2-methyl 1-indanone $Cr(CO)_3$ or the (-) *endo* methyl isomer (3), the same route was developed, taking advantage of the stereochemical control (the absolute configurations are shown in the scheme).


Cr
CH3
1
O
2
3
4
5
6
7
8
OH
HO
H
≡
Cr(CO)3
12
13
14
15

After annulation the two diastereoisomeric α-enones were obtained : (-) 4 (mp 170°, $[\alpha]_D$ = - 1040°)(12) and (-) 5 (mp 192°, $[\alpha]_D$ = - 1088°). Upon dehydration of the two active keto alcohols, (-) 8 ($[\alpha]_D$ = - 333°) was isolated. Demetallation finally gave *enantiomers with known absolute configuration*, starting from the *diastereoisomers* (-) 4 and (-) 5. Thus (-) 4 gave (-) 16 ($[\alpha]_D$ = - 210°). From (-) 8, the non conjugated enone (+) 17 ($[\alpha]_D$ = + 27°) was obtained. Similar reactions were carried out on (-) 1-tetralone $Cr(CO)_3$ and derivatives (3) leading to the two α-enones (-) 12 (mp 174°, $[\alpha]_D$ = - 2250°) and (-) 13 (mp 160°, $[\alpha]_D$ = - 1890°). After demetallation (-) 13 gave the enantiomer (+) 18 ($[\alpha]_D$ = + 440°). From the keto alcohol (-) 14 (mp 122°, $[\alpha]_D$ = - 752°) the enone (-) 15 (mp 158°, $[\alpha]_D$ = - 726°) and, after demetallation, (+) 19 ($[\alpha]_D$ = + 24°) were obtained.

The reaction sequences reported show new applications of optically active indanone- and tetralone $Cr(CO)_3$ as key intermediates for stereochemical studies. This unusual cyclization due to complexation by the $Cr(CO)_3$ moiety leads to compounds which are not available via other routes. The above sequences provide striking examples in which the reaction pathways change entirely upon conversion of a benzene ring into a benchrotrene unit. Properties of this new type of compounds are currently under further investigation.

References and notes

(1) For example see : J. APSIMON, *the Total Synthesis of Natural Products, Wiley, New-York (1973).*

(2) For a recent review of annulation methods see : M.E. JUNG, *Tetrahedron, vol. 32, 3 (1976).*

(3) G. JAOUEN and A. MEYER, *J. Amer. Chem. Soc., 97, 4667 (1975).*

(4) The two isomers are in equilibrium even with a weak base.

(5) C.D. De BOER, *J. Org. Chem., 39, 2426 (1974).*

(6) With acrylaldehyd, acrylonitril, the two isomers are obtained with the ratio Me *exo*/Me *endo* = 13/87, while using acrylester a stronger base was necessary (Triton B) and in a rapid stereospecific reaction the *endo* isomer was synthetized $\delta_{CH_3\ endo}$ 1.43.

(7) G. JAOUEN, O. HOFER and A. MEYER, *to be published.*

(8) a) W.S. TRAHANOVSKY and R.J. CARD, *J. Amer. Chem. Soc., 94, 2897 (1972).*

b) G. JAOUEN, A. MEYER and G. SIMONNEAUX, *J.C.S. Chem. Comm., 813 (1975).*

(9) a) A. CECCON and G. CATELANI, *J. Organometal. Chem., 72, 179 (1974).*

b) A. CECCON, *J. Organometal. Chem., 72, 189 (1974).*

(10) The other keto alcohol was observed only in traces by tlc.

(11) Attempts to activate the carbon in β position in 2-tetralincarboxylic acid methyl ester $Cr(CO)_3$ *exo* or *endo* and further classical alkylation failed. Starting from the pure isomers only a mixture of these isomers was recovered without any alkylation.

(12) The $[\alpha]_D$ values are given in $CHCl_3$ and at 22°. Polarimeter PERKIN-ELMER 241 MC.