Stereospecific 6-Alkylation of Oestradiol Derivatives *via* $Cr(CO)_3$ Complexes

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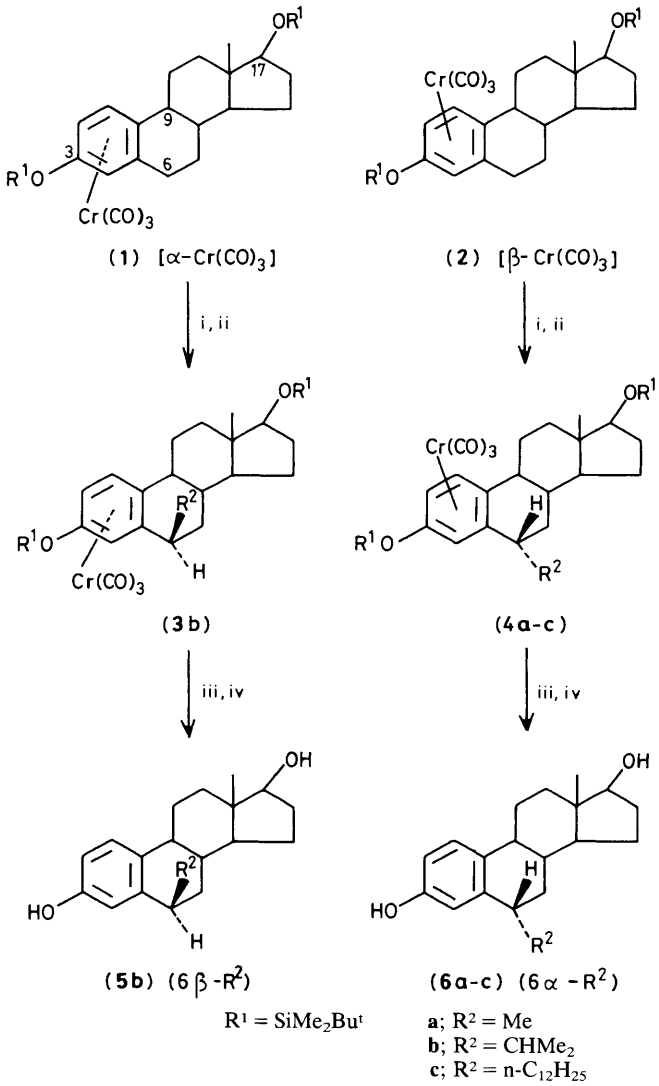
The increased kinetic acidity of benzylic hydrogen atoms of aromatic steroids temporarily modified by the $Cr(CO)_3$ group provides access to 6-alkylated oestradiol derivatives with controlled stereochemistry; the relative binding affinities of these modified hormones with respect to the oestradiol receptor have been measured.

The attachment of cytotoxic moieties to natural oestrogens in order to carry them into hormone sensitive cells is a major goal in cancer chemotherapy because most antitumour agents suffer from a lack of specificity.[1] Alkyl substituents have been suggested as suitable probes in the search for appropriate positions in the oestradiol molecule that would be reasonably tolerant to fairly large adducts.[2] In order to explore the biological effect of modification of the 6-position of oestrogens, we have designed a stereospecific 6-alkylation reaction of oestradiol derivatives using temporary activation by $Cr(CO)_3$.[3] The enhanced reactivity of the benzylic positions due to the metal carbonyl group has previously been recognized[4] but has not been utilised in the oestrogen series.

Scheme 1 illustrates our current synthetic approach. The 3,17β-bis(t-butyldimethylsilyl) protected oestradiol tricarbonylchromium α (**1**) and β (**2**) derivatives were prepared as follows. 3-t-Butyldimethylsilyl protected oestradiol, obtained by treatment of oestradiol with an equimolar amount of NaH and Bu^tMe_2SiCl, was complexed by heating with $Cr(CO)_6$ in dibutyl ether. The mixture of the two $Cr(CO)_3$–3-Bu^tMe_2Si protected oestradiol α and β diastereoisomers was separated on a silica gel column (eluant diethyl ether–light petroleum 2:1). Each diastereoisomer was then treated with NaH and Bu^tMe_2SiCl[5] to give the products (**1**) {$[\alpha]_D^{22}$ +36.7° (*c* 0.015 g/ml, $CHCl_3$)} and (**2**) {$[\alpha]_D^{22}$ +45.3° (*c* 0.017 g/ml, $CHCl_3$)} in 45% overall yield based on the isolated complexes; ratio (**1**):(**2**) = 41:59. The identification of the diastereoisomers (**1**) and (**2**) has been ascertained by chemical correlation with



Scheme 1. i, $(Me_3Si)_2NNa$; ii, R^2X; iii, *hν*–O_2; iv, Bu^n_4NF.

3-t-butyldimethylsilyl protected oestradiol–α-$Cr(CO)_2CS$ on which an *X*-ray structural analysis has been performed.[6] On treatment with $(Me_3Si)_2NNa$[7] and Me_2CHI in tetrahydrofuran, compound (**1**) gave complex (**3b**) {$[\alpha]_D^{22}$ +12.8° (*c* 0.0012 g/ml, $CHCl_3$); 9% yield of isolated product} with the alkyl group in the 6-position of the hormone exclusively and *trans* with respect to the $Cr(CO)_3$ moiety. A similar regio- and stereo-specificity was found with the β-$Cr(CO)_3$ diastereoisomer (**2**) giving (**4a—c**) in *ca.* 30% yield. It is noteworthy that in the β-complex, the 6 and 9 benzylic sites are available for proton abstraction but only products corresponding to attack at the 6 position have been observed.

Interestingly, when two potential sites of attack are present in the same complexed molecule, *e.g.* the *meta* and *para* positions with respect to the methoxy substituent, in 1-methoxy-3,4-dimethylbenzene–$Cr(CO)_3$, only products resulting from attack at the *meta* carbon atom are produced,[8] while the 4-methyl group remains unchanged. The results obtained with this simple molecule are directly transferable to more complex derivatives such as oestrogens. While stereospecific reactions are not unusual in $Cr(CO)_3$ complexes,[3,4] regiospecific pathways still remain relatively poorly documented with the exception of some direct nucleophilic attacks on $Cr(CO)_3$ modified rings.[9]

Table 1. Relative binding affinity (R.B.A.) of oestradiol and its 6-substituted derivatives.

	R.B.A. (%)
Oestradiol (E_2)	100
6α-Me-E_2 (**6a**)	31
6α-Pr^i-E_2 (**6b**)	11.4
6β-Pr^i-E_2 (**5b**)	1.6
6α-n-$C_{12}H_{25}$-E_2 (**6c**)	<0.1

Finally, decomplexation of (**3**) and (**4**) by exposure to sunlight and air,[10] followed by deprotection with Bu_4NF furnished the 6-alkyl substituted hormones (**5b**) and (**6a—c**) in 60—80% yields.†

Starting from the pair of diastereoisomers (**1**) and (**2**), it appears that a range of 6-substituted oestradiols with completely controlled stereochemistry is readily accessible. Previously this class of compounds was not generally accessible.[11] Therefore, we have performed receptor binding assays using tritium labelled oestradiol as a tracer and lamb uterine cytosol as a source of oestradiol receptor (Table 1).[12] These data show a clear discrimination between the α- and β-alkyl derivatives. While the β site appears more sensitive to steric hindrance, the 6α-alkyl substitution leads to products that maintain a reasonable affinity for the receptor providing the attached groups are not too bulky. Therefore, it seems possible to attach alkyl groups at the 6-position and still preserve some degree of affinity for the receptor.

Received, 3rd February 1984; Com. 148

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† All new compounds gave satisfactory spectroscopic data. M.p. data: (**1**) 255, (**2**) 253, (**3b**) 192, (**4a**) 242, (**4b**) 158, (**4c**) 84, (**5b**) 156, (**6a**) 130, (**6b**) 130, and (**6c**) 65 °C.