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AN ENANTIOSELECTIVE SYNTHESIS OF A 6,7-BENZOMORPHAN THROUGH THE CYCLISATION OF THE CHROMIUM TRICARBONYL COMPLEX OF AN 1-(AMINOETHAN-2'-YL)-1,2-DIHYDRONAPHTHALENE

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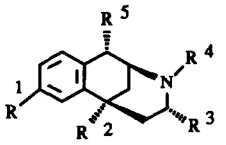
SUMMARY: (-)1(*S*),2(*S*),4(*R*),6(*R*)-1,2,3,4,5,6-Hexahydro-2,6-methano-8-methoxy- 1,3,4,6-tetramethyl-3-benzazocine has been synthesised in 86 % enantiomeric excess from the α-(η^6-chromium tricarbonyl) complex of 1(*S*),1'(*R*)-1,2-dihydro-7-methoxy-1,4-dimethyl -1-(*N*-methyl-*N*-trifluoroacetamido-1'-methylethan-2'-yl)naphthalene. A precursor of this compound is 2(*R*),4(*S*)-4-(3-methoxyphenyl)-2,4-dimethylcyclohexanone which was obtained through an Enders' type *C*-methylation reaction of 4-(3-methoxyphenyl)4-methylcyclohexanone using SAMP as the reagent.

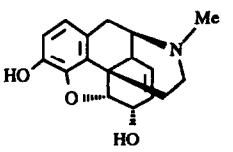
6,7-Benzomorphans (1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines) (1) represent an important class of analgesic drugs, and their syntheses have attracted the attention of many organic chemists[1]. This interest is maintained today because of more refined knowledge of the biological receptor sites at which these drugs react *in vivo*[2] and the application of computer graphics in addressing structure-activity relationships. Apart from a few notable examples,[3] routes to benzomorphans are tedious, take little account of stereochemical control, and lead to racemic products. It is known, however, that small changes in stereochemistry initiate wide fluctuations in pharmacology[4], and that the *laevo* antipodes, related to morphine (2), are significantly more potent than their enantiomers.[5]

We now describe a synthesis of the benzomorphan (13), which has the morphine absolute stereochemistry, utilising a η^6-chromium complex to promote *both* an unusual intramolecular cyclisation of the dihydronaphthalene (11), and to control the stereoselectivity of the reaction. The cyclohexanone (3) (see note) was reacted with SAMP[6] at 60°C, to give the hydrazones (4) in 93%. These were treated with KDA (potassium diisopropylamide) and methyl tosylate in dry diethyl ether at -100°C to afford the diastereomeric hydrazones (5) which, without purification, were then converted into the corresponding methiodide salts and hydrolysed by reaction with a mixture of 3M HCl and n-pentane (the biphasic system

was adopted to minimise exposure of the product ketones to aqueous acid). Column chromatography on silica of the hydrolysis products gave the *trans*-methylcyclohexanone (6), the *cis*-isomer (7) and a mixture of the two isomers in 40%, 13%, and 12% yields respectively. A series of ^{1}H NMR studies using (*R*)(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating reagent, show that the *trans*-compound was formed in an enantiomeric excess of 70%.

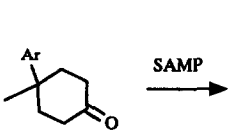


(1)

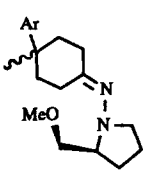


(2)

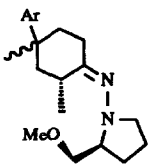
This compound was converted into the oxime which was shown to exist solely as the *E*-isomer (8) by X-ray crystallography. A Beckmann rearrangement initiated with phosphorus oxychloride in pyridine at 0°C then afforded the caprolactam (9, R=H), which was *N*-alkylated by reaction with sodium hydride, followed by the addition of methyl iodide, to give the *N*-methylcaprolactam (9, R=Me). Further reaction with methyl lithium and then entrapment of the anion so formed with trifluoroacetic anhydride gave the trifluoroacetamide (10) in 42% yield, for four steps. Cyclisation to the dihydronaphthalene (11) was achieved by heating the trifluoroacetamide with 5M hydrogen chloride in dry dioxane at 70°C (yield 88%). Finally the dihydronaphthalene was activated by complexation with chromium hexacarbonyl to give a mixture of the α- and β-chromium tricarbonyl complexes (10:1 ratio, determined by ^{1}H n.m.r.: interestingly, an X-ray determination shows that the amide unit of the dihydronaphthalene (11) is folded over the aromatic π-system). The complexes were separated and the α-isomer (12) cyclised to the corresponding chromium derivative of the benzomorphan (13) through reaction with potassium carbonate in aqueous methanol and ultra-sonification over a period of 76 hours. The product was then isolated by preparative thin layer chromatography. Decomplexation gave the required tricycle (13). The yield for the cyclisation step was 39%; the specific rotation of the microcrystalline product is $[\alpha]_D^{18}$ -59 (c=1.9,$CHCl_3$), and the enantiomeric excess is 86% (determined as before). A similar reaction with the β-isomer has not been investigated because of the limited amount of material available.



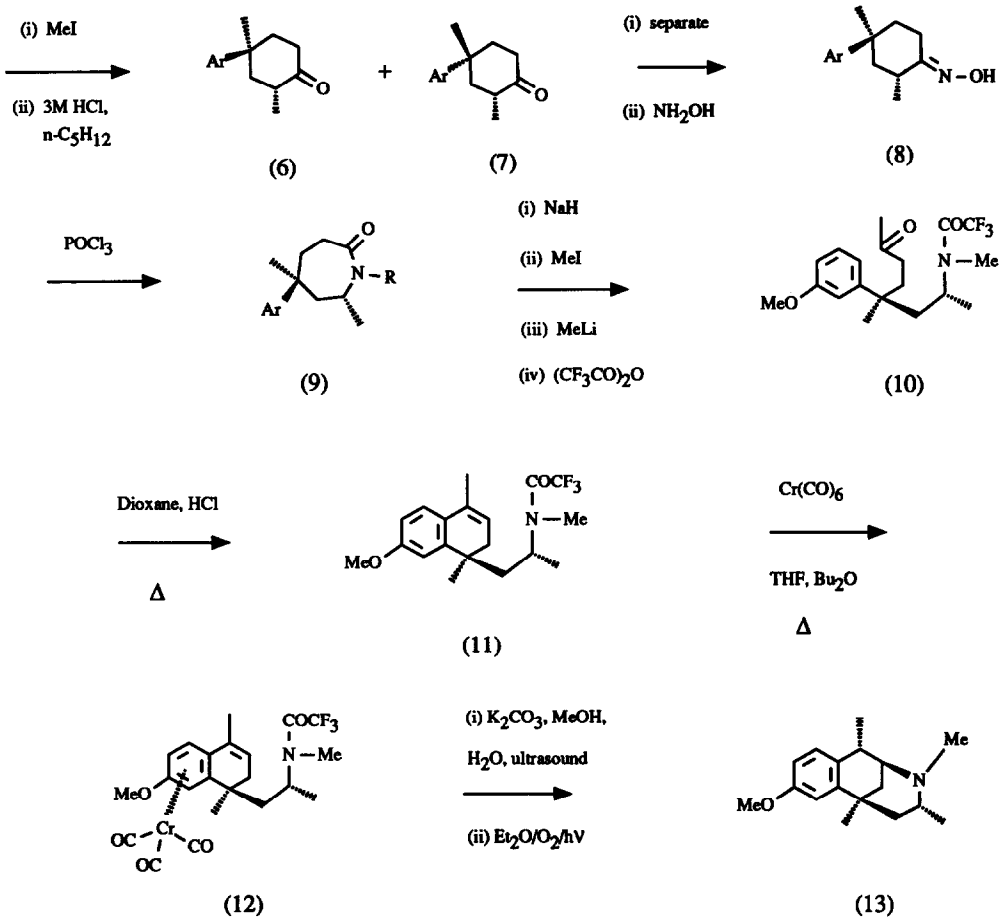
SAMP →



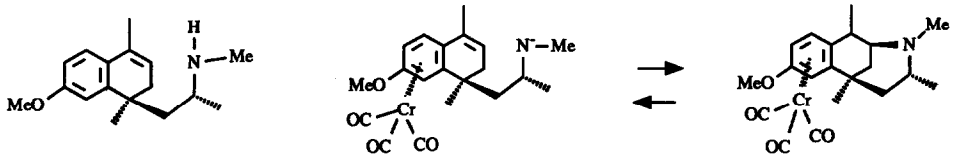
(i) KDA →
(ii) MeOTs



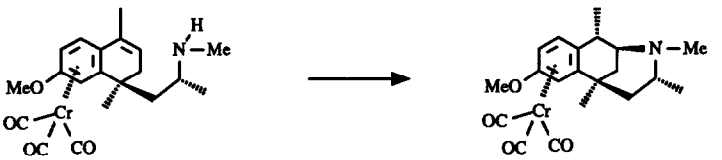
(3 , Ar=3-MeO-C_6H_4) (4) (5)



In some preliminary experiments the amine (14) was reacted with chromium hexacarbonyl to give the corresponding α- and β-complexes in the ratio 2:1. The α-complex was treated with ^{t}butyl lithium in the expectation of forming the anion (15). This we assumed would equilibrate with the tricyclic carbanion (16), however, attempts to trap the carbanion by protonation, or by reactions with methyl iodide, or with dimethyl disulphide failed. The β-complex behaved similarly. Either complexation involves the amino function or, as in a literature precedent[7] involving intermolecular reactions between nucleophiles and similar η^6-complexes, carbanion formation is only favoured at low temperature. Repetition of our experiments at temperatures as low as -100°C also met with failure. In the successful reaction recorded above, however, complexation of the trifluoroacetamide (11) ensures the formation of an arene metal bond. The protic conditions employed then hydrolyse the amide protecting group and release the complex (17), the amine function of which then attacks the electron depleted double bond, prior to stereoselective protonation *anti* to the metal atom, to give the benzomorphan derivative (18). The importance of chromium complexation is shown by the fact that treatment of the uncomplexed trifluoroacetamide (11) with potassium carbonate in aqueous methanol leads only to the formation of the amine (14).



(14) (15) (16)



(17) (18)

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3. see: for example, M.Kitamura, Yi Hsiao, R.Noyori, and H.Takaya, *Tetrahedron Letters*, **28**, 4829 (1987).
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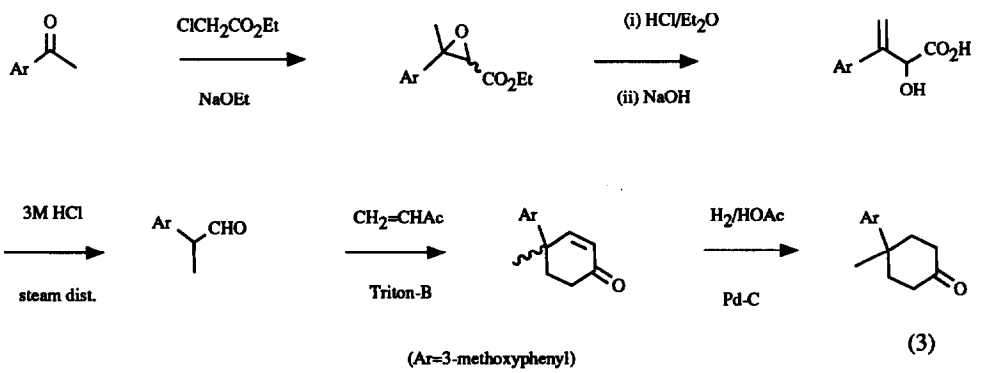
Note The starting material for the synthesis is the 4-(3-methoxyphenyl)cyclohexanone (3), which was obtained by the following route [for related work see F.Nerdel and H.Frölich, *Chem.Ber.*, **85**, 171 (1952) and F.G.Bordwell, R.R.Frame, R.G.Scamehorn, J.G.Strong, and S.Meyerson, *J.Amer.Chem.Soc.*, **89**, 6704 (1967)]. The overall yield of the cyclohexanone from 3-methoxyacetophenone was 33%.



(Ar=3-methoxyphenyl)

(3)

ACKNOWLEDGEMENTS

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