Iron-mediated Synthesis of Homochiral 4-Methylcyclohexenone Derivatives from *p*-Menthoxytoluene

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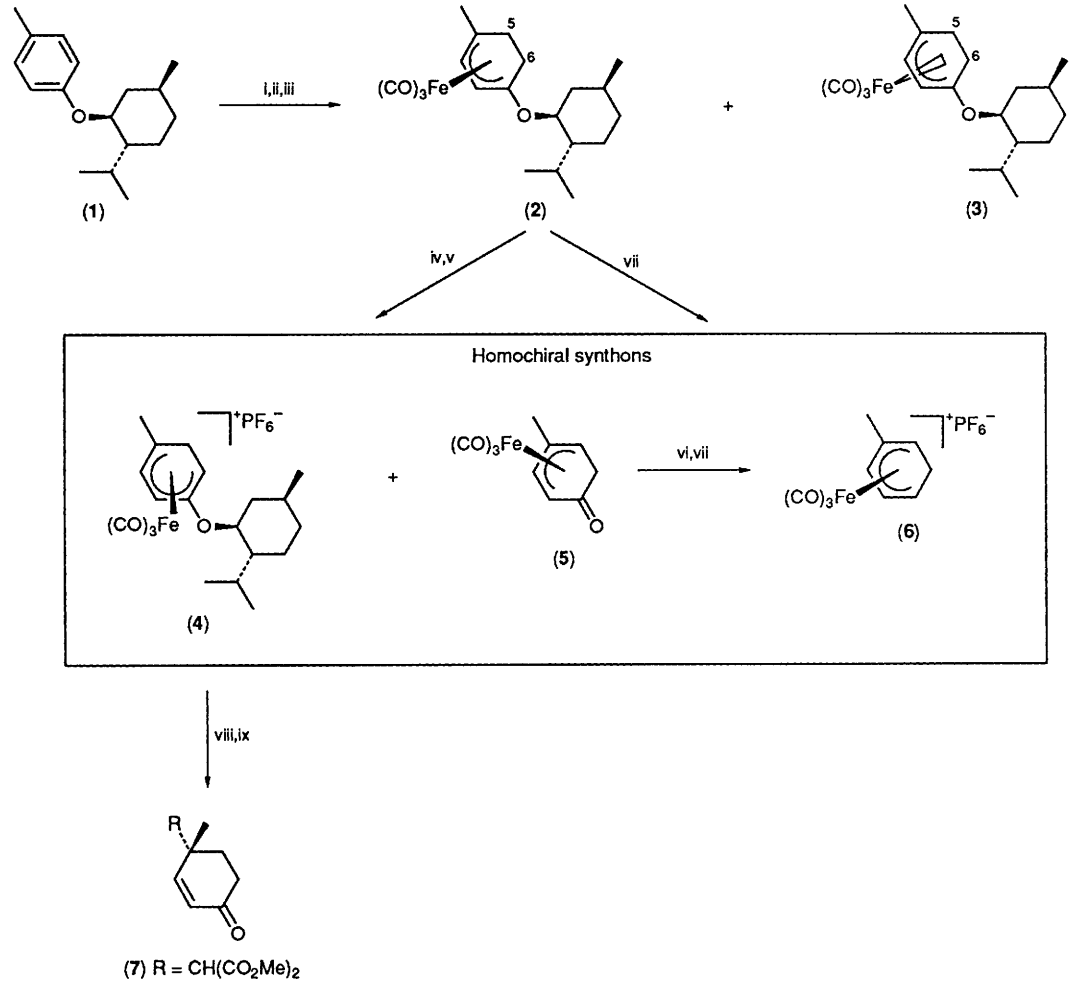
The tricarbonyl(2-menthoxy-5-methylcyclohexadienylium)iron hexafluorophosphate (**4**) prepared from *p*-menthoxytoluene can be obtained as a single diastereoisomer and displays excellent regioselectivity with a model nucleophile providing a route to homochiral 4-substituted 4-methylcyclohex-2-enones; other related homochiral synthons are also prepared.

4-Methylcyclohexenone derivatives are of prime importance as synthetic intermediates since they lead to several classes of natural products, particularly terpenes. Our interest in this area has been the synthesis of compounds which incorporate the 4-methylcyclohexenone group, present in the *A*-ring of important steroid hormones, as potential drugs for the treatment of hormone-dependent cancers.

The use of tricarbonyliron complexes of cyclohexadienes has greatly facilitated access to methylcyclohexenones, amply demonstrated by the work of Birch[1] and Pearson,[2] however it is essential that the products can be made in homochiral form. Although the requisite synthon (**8a**) has been prepared in chiral form, the route, which employs first resolution of the nor-methyl complex, then introduction of the methyl group, is circuitous.[3] This complex also suffers from the disadvantage of producing regioisomers upon nucleophilic attack.[4] We were consequently prompted to seek a more convenient procedure. Our approach has been to incorporate menthol as an integral part of the synthon (Scheme 1).

Accordingly *p*-(1*S*,2*R*,5*S*)-menthoxytoluene (**1**),† an oil, b.p. 140 °C at 4 mmHg {$[\alpha]_D$ +96° (*c* 0.5, $CHCl_3$)}, was prepared in 60% yield by heating the copper(I) alkoxide of (+)-menthol with *p*-iodotoluene using the method of Whitesides *et al.*[5] Birch reduction and iron complexation, under essentially the conditions developed by Pearson for the methoxy analogue,[6] gave a mixture of diastereoisomers, which have the iron co-ordinated to opposite sides of the diene ligand, in 74% combined yield with a 7% excess of the (1*R*,4*S*)-diastereoisomer (**2**) over (**3**) (Scheme 1). From this mixture only the diastereoisomer (**2**)† crystallised {24% overall yield from (**1**); m.p. 96—97 °C (from MeOH); $[\alpha]_D$

† New compounds isolated gave satisfactory elemental analyses.



Scheme 1. *Reagents*: i, Li, NH_3, Bu^{t}OH–tetrahydrofuran(THF); ii, *p*-$MeC_6H_4SO_3H$; iii, $Fe(CO)_5$, Bu_2O; iv, $Ph_3C^+PF_6^-$, CH_2Cl_2; v, MeOH–H_2O; vi, $NaBH_4$, EtOH; vii, H_2SO_4 then NH_4PF_6; viii, $NaCH(CO_2Me)_2$, THF; ix, $CuCl_2$, H_2O–EtOH.

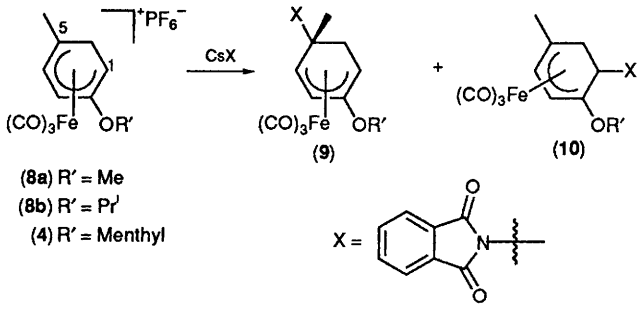
+5.6° (*c* 4, $CHCl_3$)} and it did so consistently; the other remained as an oil.

Hydride abstraction from complex (**2**) with trityl hexafluorophosphate occurred at both C-5 and C-6 (ratio 38:62); surprisingly C-6 abstraction was preferred despite the steric bulk of both the menthyl group and abstracting cation (*cf.* reaction with nucleophiles below) implying that electronic control[4] is dominant. Recrystallisation from methanol–water afforded (**4**)† as yellow crystals, m.p. 179—181 °C {42% yield from (**2**); $[\alpha]_D$ −199° (*c* 0.4, MeCN)}. The product resulting from abstraction at C-5 was hydrolysed in the recrystallisation step to give the cyclohexadienone complex (**5**) as an orange oil {25% yield from (**2**); $[\alpha]_D$ +558° (*c* 0.1, $CHCl_3$)} in homochiral form,‡ and therefore also a useful chiral synthon {lit.,[7] for partially resolved complex: $[\alpha]_D$ +219° (*c* 0.2, $CHCl_3$).}

In order to assign the absolute configuration, the complex (**2**) was treated with sulphuric acid to promote proton shift[6,8] from the 5-position and menthol elimination. This gave the known complex (**6**) in 68% yield for which Birch and co-workers have unambiguously assigned the configuration through conversion to the terpene α-phellandrene.[7] The complex (**6**) had $[\alpha]_D$ +23.9° (*c* 1, MeCN) corresponding to 80% enantiomeric excess (e.e.), a value considerably greater than that for the sample prepared by Birch {$[\alpha]_D$ +0.6° (*c* 3, MeCN)} following an asymmetric complexation procedure. This complex is additionally a valuable synthon for terpene synthesis and it has also been prepared {$[\alpha]_D$ +25.1° (*c* 1, MeCN)} by Stephenson *et al.*, in a multi-step procedure from the dihydrodiol obtained through microbial oxidation of toluene.[9] Although the enantiomeric purity of our complex was high, some racemisation would have occurred through proton shift *via* the 6-position in (**2**).[7,8] The homochiral complex (**6**) {$[\alpha]_D$ +29.8° (*c* 1, MeCN)} was prepared in an unambiguous manner from the cyclohexadienone complex (**5**) by sodium borohydride reduction[10] followed by treatment of the resulting crystalline alcohol† {m.p. 85—86 °C; $[\alpha]_D$ +80.6° (*c* 0.6, $CHCl_3$); $\nu_{max.}$ 3308, 2044, and 1973 cm^{-1}} with sulphuric acid.

Nucleophilic attack on the chiral synthon (**4**) by dimethyl malonate anion proceeded in an enantiospecific fashion, on the face opposite to the iron, and exclusively at the C-5 position, as expected.[11] Decomplexation of the resultant iron diene complex† {m.p. 80.5—81.0 °C; $[\alpha]_D$ +66.1° (*c* 0.4, $CHCl_3$)} followed by hydrolysis of the menthoxy diene liberated the homochiral‡ (*R*)(−)-4-substituted 4-methyl-

‡ Only a single species was observed by NMR spectroscopy in the presence of Eu(tfc)$_3$ as chiral shift reagent, and the racemate showed clear duplicate signals.



Scheme 2

Table 1. Product distribution from the reaction at 20 and 70 °C of tricarbonyliron complexes (**8**) with caesium phthalimide.

	Ratio of regioisomers (**9**) : (**10**)	
Complex	At 20 °C	At 70 °C
(**8a**)	86 : 14	14 : 86
(**8b**)	95 : 5	50 : 50
(**4**)	>99 : 1	90 : 10

cyclohexenone derivative (**7**) {$[\alpha]_D$ −30.1° (*c* 0.8, $CHCl_3$); 65% yield from (**4**)} already known in racemic form.[12]

More interesting, however, was reaction of (**4**) with the caesium salt of phthalimide (Scheme 2 and Table 1) as this nucleophile has a propensity to attack the methoxy analogue (**8a**) at the unsubstituted C-1 position. Table 1 shows that when the reaction is carried out at room temperature (kinetic control) the bulky isopropyl group gives greater preference for attack at the methylsubstituted C-5 position, as found by Pearson in the case of other nucleophiles.[4] We find that the menthyl group provides even better regioselectivity as more than 99% of the required C-5 regioisomer was formed {(**9**); (R′ = menthyl),† m.p. 151—152 °C; $[\alpha]_D$ +51.3° (*c* 0.3, $CHCl_3$)}. It is noteworthy that the regioisomer distribution was found to change if the products were heated to 70 °C owing to reversibility of the addition, but the equilibrium ratios still reflect the varying bulk of the alkoxy substituents.

Owing to the presence of the methylcyclohexenone group in biologically important molecules and the variety of subsequent chemical transformations that may be performed on the enone function, the homochiral synthons (**4**)—(**6**) prepared by the methods described are expected to have considerable synthetic utility. Moreover, the ready availability of either pure enantiomer of menthol implies that either optical isomer is equally accessible. This strategy may also be applied to other organotransition metal π-complexes where until now only the methoxy complexes have been studied.[1,2]

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References

1 A. J. Birch and L. F. Kelly, *J. Organomet. Chem.*, 1985, **285**, 267.
2 A. J. Pearson, *Acc. Chem. Res.*, 1980, **13**, 463.
3 J. A. Howell and M. J. Thomas, *Organometallics*, 1985, **4**, 1054.
4 A. J. Pearson, P. Ham, C. W. Ong, T. R. Perrior, and D. C. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1527.
5 G. M. Whitesides, J. S. Sadowski, and J. Lilburn, *J. Am. Chem. Soc.*, 1974, **96**, 2829.
6 A. J. Pearson and C. W. Ong, *J. Am. Chem. Soc.*, 1981, **103**, 6686.
7 A. J. Birch, W. D. Raverty, and G. R. Stephenson, *J. Org. Chem.*, 1981, **46**, 5166.
8 A. J. Birch and M. A. Hass, *J. Chem. Soc. C*, 1971, 2465.
9 P. W. Howard, G. R. Stephenson, and S. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1988, 1603.
10 A. J. Birch, P. E. Cross, J. Lewis, D. A. White, and S. B. Wild, *J. Chem. Soc. A*, 1968, 332.
11 A. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2069.
12 A. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1255.