Complementary Stereoselective Cyclisations of *N*-(3,4-Dimethoxybenzyl)ephedrine and its Chromium Tricarbonyl Complex to *trans*- and *cis*-2,3-Dimethyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines Respectively

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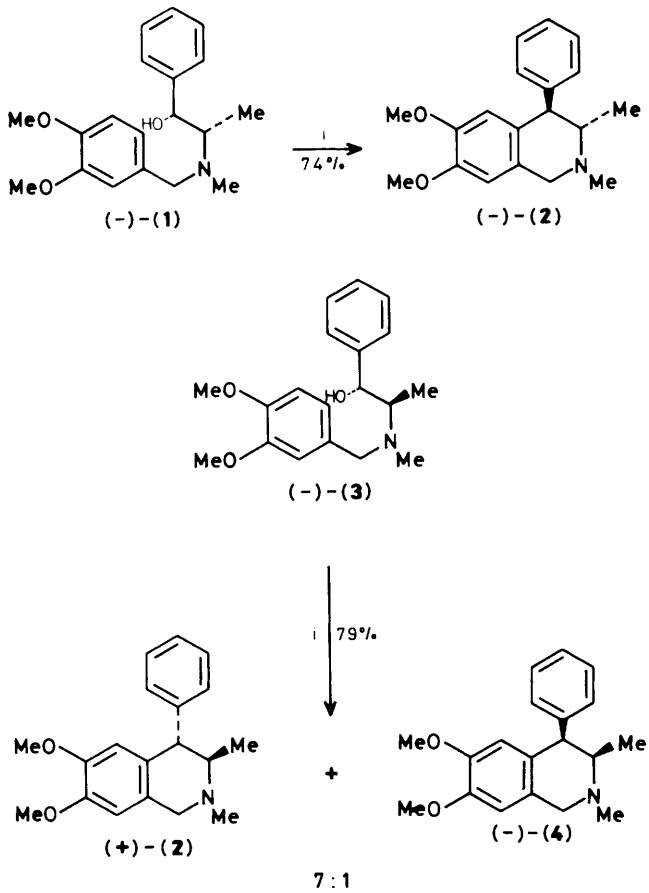
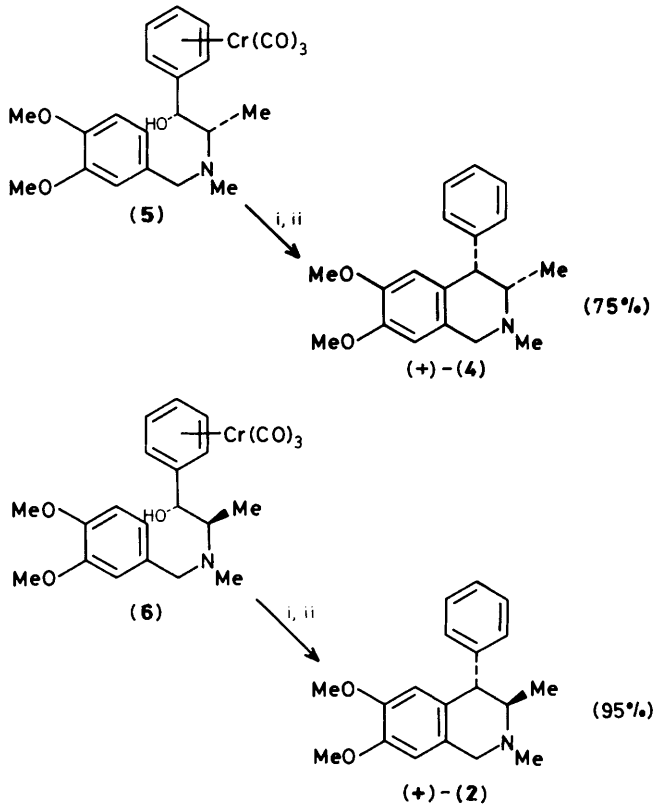
Acid promoted cyclisations of *N*-(3,4-dimethoxybenzyl)ephedrine and its chromium tricarbonyl complex occur with completely complementary stereoselectivities to give exclusively *trans*-(−)- and *cis*-(+)-2,3-dimethyl-4-phenyl-6,7-dimethoxytetrahydroisoquinolines† respectively.

A postulated biosynthesis of 4-aryl tetrahydroisoquinolines involves the acid catalysed cyclisation of *N*-benzylphenethanolamines.[1] The potent pharmacological activity of simple 4-aryl tetrahydroisoquinolines has stimulated much interest in their syntheses,[2] many of which are based on a biomimetic approach. However, to date no investigations have been reported on the stereochemical course of the acid catalysed cyclisations of *N*-benzylphenethanolamines. We describe here the stereoselective cyclisations of *N*-benzylephedrine and

† For clarity the descriptors -1,2,3,4- are omitted.



Scheme 1. *Reagents*: i, H^+.



Scheme 2. *Reagents*: i, H^+; ii, air.

pseudoephedrine derivatives to *cis*- or *trans*-4-phenyltetrahydroisoquinolines.

Treatment of (−)-*N*-(3,4-dimethoxybenzyl)ephedrine (**1**) with a mixture of trifluoroacetic and sulphuric acids (1 : 1) at reflux gave the *trans*-tetrahydroisoquinoline (−)-(**2**) {$[\alpha]_D^{20}$ −13.7° (*c* 1.25, $CHCl_3$)} completely stereoselectively. Similar acid treatment of the corresponding (−)-pseudoephedrine derivative (**3**) gave a 7 : 1 mixture of the *trans*- and *cis*-tetrahydroisoquinolines (+)-(**2**) and (−)-(**4**) which has so far proved inseparable. The relative stereochemistries of (**2**) and (**4**) were assigned by comparison of their H^3–H^4 coupling constants with those obtained for *cis*- and *trans*-3,4-dimethyltetrahydroisoquinoline derivatives.[3] The stereoselective cyclisation of (**1**) to (**2**) with complete inversion of configuration can be understood in terms of neighbouring group participation by the dimethoxyphenyl moiety in the ionisation of the protonated benzylic hydroxy group. In the cyclisation of (**3**) such participation is disfavoured by developing steric interactions between the phenyl and C-3 methyl groups and the reaction presumably, therefore, proceeds *via* a free benzylic carbonium ion which is trapped preferentially from the face leading to the thermodynamically more stable *trans*-diastereoisomer (**2**).

In (benzylalcohol)chromium tricarbonyl complexes, when the hydroxy group can adopt a conformation close to antiperiplanar to the arene–chromium axis then retention of configuration has been observed in acid promoted benzylic substitution reactions.[4] This is consistent with initial inversion to form a configurationally stable carbonium ion and subsequent trapping, with inversion of configuration, giving overall retention. Furthermore, chromium tricarbonyl stabilised benzylic carbonium ions can be trapped intermolecularly with electron-rich arenes.[5] Acid treatment of (**5**), the chromium tricarbonyl complex of the ephedrine derivative (**1**), below −20 °C proceeded stereoselectively to give, after decomplexation, only the *cis*-tetrahydroisoquinoline (+)-(**4**) {$[\alpha]_D^{20}$ +108° (*c* 0.11, $CHCl_3$)}. Similar acid treatment of (**6**), the chromium tricarbonyl complex of the pseudoephedrine derivative (**3**) at 0 °C also proceeded completely stereoselectively to give, after decomplexation, only the *trans*-tetrahydroisoquinoline (+)-(**2**){$[\alpha]_D^{20}$ +13.8° (*c* 0.24, $CHCl_3$)}. Cyclisations of both (**5**) and (**6**) are occurring, as expected with complete retention (double inversion) at the benzylic position. The two cyclisations of (−)-(**1**) and its chromium tricarbonyl complex (**5**) are complementary producing overall from (−)-ephedrine the *trans*- and *cis*-2,3-dimethyl-4-phenyl-6,7-dimethoxytetrahydroisoquinolines (−)-(**2**) and (+)-(**4**) respectively.

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References

1 C. Fuganti, 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, 1975, vol. XV, p. 141.
2 H. Hara, R. Shirai, O. Hoshino, and B. Umezawa, *Heterocycles*, 1983, **20**, 1945, and references given therein.
3 S. J. Coote, S. G. Davies, and K. H. Sutton, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1481.
4 S. Top and G. Jaouen, *J. Org. Chem.*, 1981, **46**, 78.
5 M. Uemura, T. Minami, and Y. Hatashi, *J. Organomet. Chem.*, 1986, **299**, 119.