

SYNTHESIS OF EARTHY-MOULDY SMELLING COMPOUNDS - I I ETHYL α - AND β - FENCHOLS

P. Gosselin^a, D. Joulain^b, P. Laurin^a, F. Rouessac^a

^a Laboratoire de Synthèse Organique, associé au CNRS
Faculté des Sciences, BP 535, F-72017 Le Mans, France

^b Robertet S.A., BP 100, F-06333 Grasse, France.

Summary : Several stereoselective routes to both ethyl α - and β - fenchols 1 α and 1 β are discussed. Direct addition of ethyllithium to fenchone was the best route to 1 α whereas obtention of 1 β was achieved through the highly stereoselective retroethynylation of a mixture of ethynyl α - and β -fenchols 4 α and 4 β .

In connection with studies on compounds exhibiting an earthy-mouldy olfactive characteristic, we recently reported a stereospecific synthesis of (\pm)-geosmin¹. Pursuing our investigations in this field, we looked for the best stereoselective synthesis of ethyl α -fenchol 1 α .

It is indeed worthy to note that 1 α includes all the required features for compounds exhibiting an earthy-mouldy odour¹, namely:

- a rigid bi- or tricyclic structure with 10-15 carbon atoms
- an axial or semi-axial tertiary hydroxyl group
- a methyl or gem-dimethyl group adjacent to the carbinol group.

In view of sensory comparison we also searched for the best stereoselective route to ethyl β -fenchol 1 β which has lost one of the above mentioned features: the axial orientation for the hydroxyl group.

Moreover, as it is known that olfactive properties of enantiomers may be different, we conducted our syntheses from both antipodes of fenchone 2. Our results are summarized in Scheme I (one enantiomeric serie represented, starting with (-)-fenchone).

I - Syntheses of ethyl α -fenchol 1 α

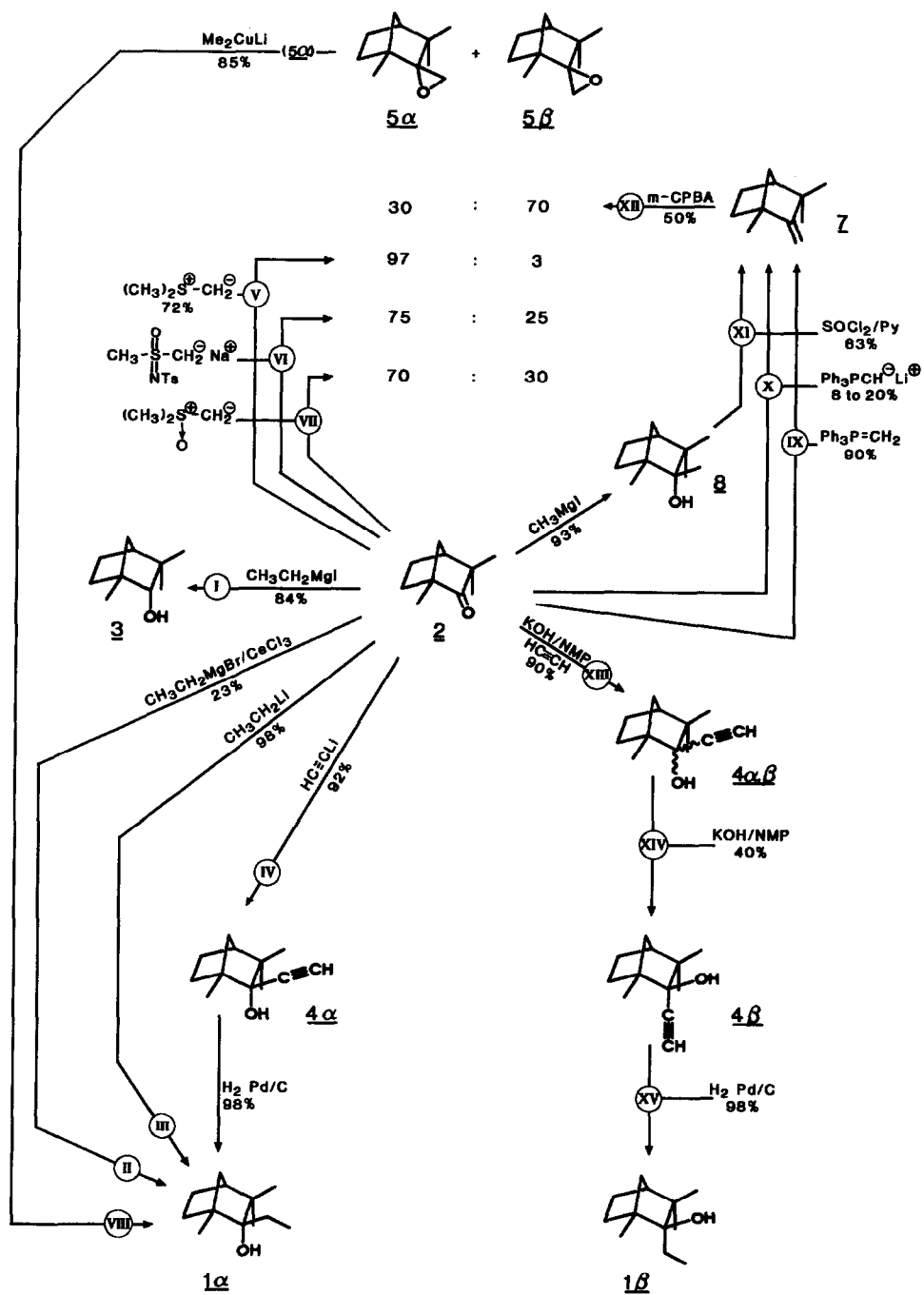
A - Reaction of organometallics with fenchone

Exo-attack of organometallic compounds from the less hindered side of bicyclo[2.2.1]heptanones unsubstituted in the 7 position, leads to endo-alcohols with generally high stereoselectivity².

As previously reported with other alkylmagnesium halides³, reactions of fenchone 2 with ethylmagnesium iodide (ether, reflux, 8 h, I Scheme I) gave mainly the reduction product, α -fenchol 3 (84%) together with 1 α (13%) and unreacted 2 (3%)⁴.

Cerium chloride promoted reaction of ethylmagnesium bromide⁵ (THF, reflux, 2 h, II Scheme I) afforded slowly but stereospecifically 1 α (23%), most of the ketone (75%)⁴ remaining unaffected.

On reaction with ethyllithium (ether, 1 h at 0°C then 3 h at 20°C, III Scheme I), fenchone led to a 97:3 mixture⁴ of 1 α :1 β respectively in 98% isolated yield which is far better than the 33% yield reported in the literature⁶.



NMP - N-Methylpyrrolidone

Scheme 1

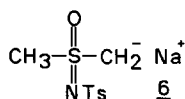
A 96:4 ratio of 4 α to 4 β was obtained⁴ through addition of lithium acetylide-ethylenediamine complex at 35°C (THF, 4 h, 95% isolated yield after distillation, IV Scheme I). When performed at 0°C, the reaction led almost stereospecifically to 4 α ($[\alpha:\beta]>99:1$)⁴, (THF, 24 h, 92% isolated yield, IV Scheme I)⁷. Catalytic hydrogenation of 4 α (H₂, 10% Pd/C, AcOEt, 4 h) afforded 1 α in 98% isolated yield.

B - Syntheses of 1-methylcamphene-endo-epoxide 5 α

We next examined three routes to epoxide 5 α (Scheme I) the synthesis of which has not yet been reported.

a) Slow addition of fenchone 2 (2 g/h) to dimethylsulfonium methylide⁸ (3 equiv., DMSO, 0°C then 2 h at 20°C, V Scheme I) afforded a 97:3 mixture⁴ of unstable epoxides 5 α (endo):5 β (exo) respectively, in 72% yield after distillation (Eb₁₃ = 76-8°C)⁹.

b) Welch *et al*¹⁰ reported the exclusive formation of the *endo* epoxide when reacting norbornanone with one equivalent of S-methyl-S-(sodiummethyl)-N-(4-tolylsulfonyl)sulfoximide 6. In our hands, with fenchone, reaction of anion 6 was still incomplete after 90 h at 50°C but GC examination of an aliquot, already showed a 3:1 mixture of epoxides 5 α :5 β respectively, together with several unidentified products (VI, Scheme I).



c) Reaction of fenchone with dimethylsulfoxonium methylide⁸ (VII, Scheme I) was first designed for the synthesis of *exo* epoxide 5 β ¹¹. This very slow reaction but proved to give mainly the *endo* epoxide 5 α although with moderate stereoselectivity: after stirring for 3 days at 50°C, the crude product contained a 46:21:33 mixture⁴ of 5 α :5 β :2(unreacted), respectively.

The best stereoselective synthesis of 5 α was then by far the reaction of fenchone 2 with dimethylsulfonium methylide¹².

Upon treatment with lithium dimethylcuprate (ether, reflux, 72 h, VIII Scheme I), epoxide 5 α was readily converted to ethyl α -fenchol 1 α in 85% yield, thus confirming the *endo* stereochemistry of epoxide 5 α .

However, it appeared from these attempts that the most convenient route to 1 α remained the one-step addition of ethyllithium to fenchone (III, Scheme I).

II - Syntheses of ethyl β -fenchol 1 β

A - Syntheses of 1-methylcamphene-exo-epoxide 5 β

A stereoselective route to the yet unreported ethyl β -fenchol 1 β was then envisioned through the epoxidation of methylcamphene 7 with *m*-chloroperbenzoic acid (*m*-CPBA).

Among the numerous procedures described for the synthesis of 7, best results are by far obtained through the reaction of methylenetriphenylphosphorane with fenchone, according to the excellent procedure recently reported by Fitzer and Quabeck¹³ (*t*-BuOK, benzene, 120°C, 7 h, IX Scheme I).

As a matter of fact, use of α -lithiomethylenetriphenylphosphorane¹⁴ (X, Scheme I) proved to be quite unsatisfactory, yielding only poor yields of methylcamphene 7. It should be quoted that problems are sometimes encountered when using this reagent¹⁵.

Dehydration of methylfenchol 8 by treatment with either KHSO₄¹⁶, Ac₂O¹⁶ or SOCl₂¹⁷ afforded moderate quantities of 7 together with hardly separable rearrangement products (XI, Scheme I).

Unfortunately, epoxidation of 7 with *m*-CPBA (NaHCO₃, CH₂Cl₂, 1 h, 0°C, XII Scheme I) afforded a 7:3 mixture of unstable epoxides 5 β (*exo*):5 α (*endo*) respectively. It was consequently impossible to directly gain access to pure *exo* epoxide 5 β .

B - Reversibility of the ethynylation of fenchone

We next studied the selective degradation of the 1:1 mixture of α - and β - ethynylfenchols 4 α , 4 β , obtained in 90% yield according to Chodkiewicz *et al* ⁷ (C₂H₂, KOH, N-Methylpyrrolidone, 25°C, 56h, XIII Scheme I). The crude mixture resulting from this ethynylation was treated with grounded dry KOH (XIV Scheme I) and the progress of the reaction monitored by GC. Results obtained through different reaction conditions are summarized in the following table.

Starting Mixture (GC%)			KOH (equiv.)	Θ (°C)	t (h)	Products (GC%)		
<u>4α</u>	<u>4β</u>	<u>2</u>				<u>4α</u>	<u>4β</u>	<u>2</u>
44	46	10	2	50	1	0	0	100
			2	20	4	7	31	62
			1	20	4	0.6	40	59

Highly selective degradation of 4 α was then possible provided that only one equivalent of KOH was used at 20°C¹⁸. Fenchone was not separated at this stage, but the mixture was directly hydrogenated (H₂, Pd/C, EtOAc, 20°C, 5 h, XV Scheme I). Ethyl β -fenchol 1 β was separated from fenchone through liquid chromatography on

alumina (Activity I + 3% w/w H₂O, 99:1 cyclohexane:ethylacetate).

Starting from both (+)- and (-)-fenchones we have thus obtained (+)- and (-)-ethyl α -fenchols 1 α and ethyl β -fenchols 1 β . Analytical samples, of suitable purity for olfactory screenings, were obtained through preparative gas chromatography (10% Carbowax 20M on Volaspher A2 (Merck)) and are now being evaluated.

References and Notes

- 1 - Gosselin, P.; Joulain, D.; Laurin, P.; Rouessac, F. *Tetrahedron Lett.* **1989**, *30*, 2775 and references therein.
- 2 - Kropf, H. In *Houben-Weyl*, 4th ed.; Thieme: Stuttgart, 1980; Vol. VI/1a, p 1216.
- 3 - Kowola, J. *Suomen Kemistilehti.* **1973**, *B46*, 212.
- 4 - Ratios refer to mole % obtained by GC of the product.
- 5 - Imamoto T.; Takiyama N.; Nakamura K. *Tetrahedron Lett.* **1985**, *26*, 4763.
- 6 - Pallaud, R.; Pleau, J. *C. R. Acad. Sci. Paris* **1967**, *265C*, 1479.
- 7 - Ethynyl α -fenchol 4 α was previously obtained by addition of sodium or bromomagnesium acetylide to fenchone in yields limited to 76% and 50% respectively: Chodkiewicz, W.; Capmau, M. L.; Boissard-Gerde, M. *Ibid.* **1968**, *267C*, 911.
- 8 - Corey, E.J.; Chaykovsky, M. *J. Amer. Chem. Soc.* **1965**, *87*, 1353.
- 9 - All spectral data are in agreement with the structures assigned to new compounds.
- 10 - Welch, S.C.; Prakara Rao, A.S.C.; Lyon, J.J.; Assercq, J.M. *J. Amer. Chem. Soc.* **1983**, *105*, 252.
- 11 - Bessière-Chrétien, Y.; Elgaied, M.M.; Meklati, B. *Bull. Soc. Chim. Fr.* **1972**, 1000 and references therein.
- 12 - Even stored at 0°C, unstable epoxides 5 α and 5 β rearrange slowly into two new compounds whose structures are now under investigation.
- 13 - Fitzer, L.; Quabeck, U. *Synthetic Commun.* **1985**, *15*, 855.
- 14 - Corey, E. J.; Kang, J. *J. Amer. Chem. Soc.* **1982**, *104*, 4724.
- 15 - a) Schlosser, M.; Schaub, B.; Jenny, T. *Tetrahedron Lett.* **1984**, *25*, 4097.
b) Schlosser, M.; Schaub, B. *Ibid.* **1985**, *26*, 1623.
- 16 - Antkowiak, W. Z. *Bull. Acad. Polon. Sci., Serie Sci. Chim.* **1966**, *14*, 437.
- 17 - Dimmel, D.R.; Fu, W.Y. *J. Org. Chem.* **1973**, *38*, 3778.
- 18 - Such a degradation, although less selective, was reported previously about epimeric ethynyl-borneols and camphor.¹⁹
- 19 - Chodkiewicz, W.; Capmau, M. L.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1968**, 3323.

(Received in France 5 March 1990)