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First synthesis of (−)-(1*R*,4*R*)- and (+)-(1*S*,4*S*)-(7,7-dimethyl-2-methylene-bicyclo[2.2.1]hept-1-yl)-methanol: new fenchone-derived chiral auxiliaries

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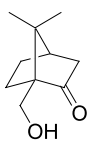
Abstract—The treatment of (+)- or (−)-fenchones epoxides with 1:2 85% H_3PO_4:DMSO for 30 min at 20°C induced an enantiospecific Wagner–Meerwein rearrangement affording new C(10)-*O*-substituted camphor derivatives which could prove useful as chiral auxiliaries. © 2001 Elsevier Science Ltd. All rights reserved.

Bicyclic optically active derivatives of (*R*)-(+)-camphor have become of widespread use as chiral auxiliaries[1] as well as starting materials in asymmetric synthesis.[2] Among these, since the pioneering work of Oppolzer,[1] C(10)-substituted derivatives have been found to be of particular interest. Readily available 10-camphorsulfinic acids have been used as the starting material for the preparation of the majority of these derivatives which, consequently, have a sulphur atom attached to C(10).

García Martínez et al.[3] recently emphasized that other C(10)-heterosubstituted camphor derivatives have been prepared and tested as valuable chirality sources, among which C(10)-*O*-derivatives deserve special attention. These factors led these authors to finalise an efficient new preparation of 10-hydroxycamphor **1**.

These results prompted us to report herein our own findings in that field: a two step, enantiospecific preparation of alcohol **2**, which is another potentially interesting C(10)-*O*-substituted camphor derivative.



1

(-)-2

(+)-2

We previously reported[4] on the preparation of ethyl α- and β-fenchols from fenchone **3**. Among the several routes we tried, one involved the (then unknown) α- and β-fenchone epoxides **4**, which were thus prepared for the first time. However, we stated that 'even stored at 0°C, unstable α- and β-epoxides rearrange slowly into two compounds whose structures are now under investigation'.

Indeed, after heating overnight in refluxing chloroform (0.6 M solution) under argon, epoxides **4** (α:β 97:3) were fully transformed (GC monitoring) into three new compounds which were easily separated by liquid chromatography on silica gel (cyclohexane:ethyl acetate, 96:4) and characterized as aldehyde **5**[5] (α:β 1:3, 53%, not separated) and the as yet unreported alcohol **2**[6] (47%).

In order to explain the formation of **2** and **5**, the plausible route depicted in Scheme 1 can be considered. Traces of HCl dissolved in chloroform could protonate the epoxides **4** whose strain would then be released by opening into the tertiary carbocation **6**. The latter could next react following two pathways. Direct proton elimination (A) would afford the enol tautomer of aldehydes **5**. According to the other pathway (B), a Wagner–Meerwein rearrangement would lead to another tertiary carbocation whose stabilisation through proton elimination would then afford alcohol **2**. It is worth noting that, under these conditions, the isomeric alcohol **7** was not detected.

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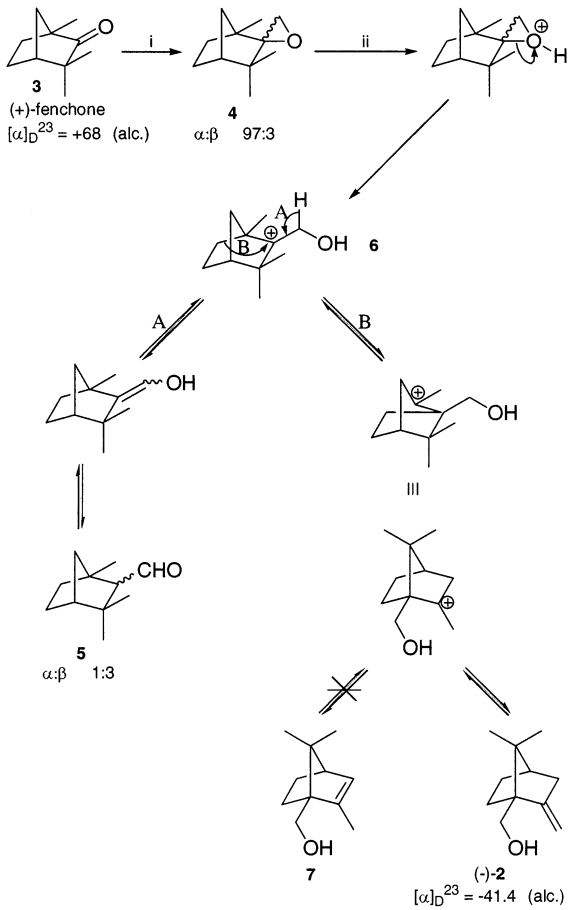

Scheme 1. *Reagents and conditions*: (i) 3 equiv. of dimethylsulfonium methylide, DMSO/THF, −5°C, 1 h;[4] (ii) $CHCl_3$, reflux, 21 h (Table 1, entry 1). Starting from (−)-fenchone of $[\alpha]_D^{23} = -57.0$, the same sequence afforded (+)-**2** of $[\alpha]_D^{23} = +25.9$.

As emphasized above, due to the interesting structural features of alcohol **2**, it was deemed useful to seek conditions that could favour its formation over that of aldehydes **5** (Table 1).

In this respect, Lewis acids (Table 1, entries 2–5) were ineffective as they mainly favoured the formation of aldehyde **5**, which is the sole product with $SnCl_4$ or Me_2AlCl.

Turning to Brønsted acids proved more successful, especially when used in conjunction with a polar solvent. The best result was thus obtained after stirring for 30 min at room temperature in a 1:2 mixture of 85% H_3PO_4 and DMSO (Table 1, entry 12). A small proportion (7%) of the isomeric alcohol **7** was formed in this case. Liquid chromatography on silica gel (cyclohexane:ethyl acetate, 96:4) allowed easy separation of aldehydes **5** but not of alcohol **7**. Alcohol **2** was therefore obtained in 65% yield from epoxides **4** as a 92:8 mixture with **7**.[8]

The enantiomeric purities of both (−)-**2** (derived from (+)-fenchone:[9] $[\alpha]_D^{23}$ +68.0 (alc.): o.p. = 0.9789) and (+)-**2** (from (−)-fenchone: $[\alpha]_D^{23}$ −57.0 (alc.): o.p. = 0.820) were determined by chiral GC analysis using a CP-Chirasil-DEX-CB capillary column (Chrompack, 25 m×0.25 mm i.d.). As shown in Fig. 1, the enantiomeric excesses measured for (−)-**2** (97.8% e.e.) and (+)-**2** (81.1% e.e.) were found to be identical to the enantiomeric purities of the starting (+)- and (−)-fenchones, respectively. Thus, the Wagner–Meerwein rearrangement occurred in an enantiospecific way.

In summary, starting from commercially available (+)- and (−)-fenchones we have developed a two-step enantiospecific synthesis of new C(10)-*O*-substituted chiral

Table 1. Acid-catalysed rearrangement of epoxides **4**[a]

Entry	Reagent	Solvent	Temp. (°C)	Time (h)	Ratio **2**:**5**:others[b]
1	HCl (traces)	Chloroform	Reflux	21	47:53
2	$BF_3{\cdot}OEt_2$ (0.2 equiv.)	Diethyl ether	Rt	2.5	15:85
3	$SnCl_4$ (1 equiv.)	Dichloromethane	−60 to −20	2	0:100
4	$Eu(Fod)_3$ (0.1 equiv.)	Chloroform	Rt	2	48:52
5	Me_2AlCl (0.5 equiv.)	Dichloromethane	−78	1	0:100
6	TsOH (0.05 equiv.)	Toluene	Rt	0.5	51:49
7	Amberlyst 15 (0.01 equiv.)	Hexane	Rt	18.5	8:92
8	3% HCl[c]	Methanol	0	0.25	56:22:22[d]
9	HCl (gas)	Diethyl ether	Rt	0.50	62:38
10	85% H_3PO_4:diethyl ether (1:1)		Reflux	6	72:11:5:12[e]
11	1 M H_3PO_4:dimethylsulfoxide (1:1)		Rt	0.25	73:10:7:10[f]
12	**85% H_3PO_4:dimethylsulfoxide (1:2)**		**Rt**	**0.5**	**82:11:7**[g]

[a] Reaction monitored by either TLC or GC. The indicated times refer to the disappearance of epoxides **4**.
[b] The product ratio was determined by both GC and 400 MHz ^1H NMR integration of the crude mixture.
[c] Anhydrous HCl in methanol prepared by the addition of acetyl chloride (1 mL) to anhydrous methanol (20 mL).[7]
[d] The addition compound of methanol on the exocyclic double bond of **2** was detected.
[e] The isomeric alcohol **7** was observed (5%) together with the diol (12%) resulting from hydration of the double bond in either **2** or **7**.
[f] Others are alcohol **7** (7%) and diol (10%).
[g] The isomeric alcohol **7** (7%) was detected.

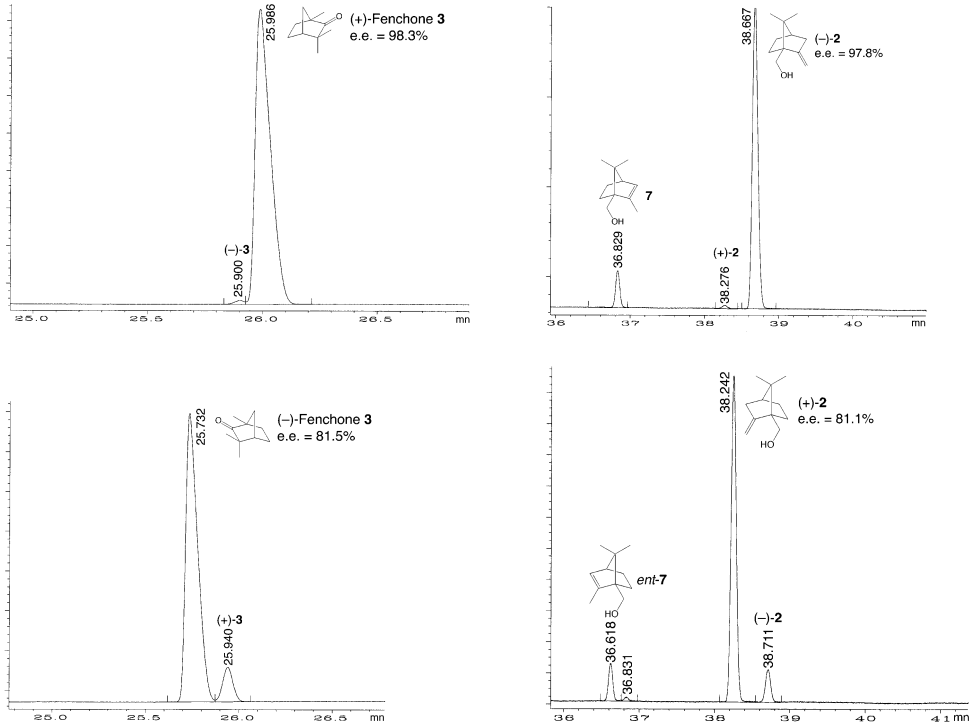

Figure 1. GLC analysis on a CP-Chirasil-DEX-CB capillary column (Chrompack, 25 m×0.25 mm i.d.) of the starting (+)- and (−)-fenchones and of the alcohols resulting from the treatment of epoxides **4** with 85% H_3PO_4 in DMSO (Table 1, entry 12). In both cases, the e.e. of the resulting alcohols **2** and **7** are found identical to the e.e. of the starting fenchones.

camphor derivatives. The possibility of the development of these derivatives as chiral auxiliaries is currently under investigation.

References

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2. Tse-Lok Ho, *Enantioselective Synthesis: Natural Products from Chiral Terpenes*; Wiley Interscience: New York, 1992.
3. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2000**, *11*, 4437 and references cited therein.
4. Gosselin, P.; Joulain, D.; Laurin, P.; Rouessac, F. *Tetrahedron Lett.* **1990**, *31*, 3151.
5. de Botton, M. *Bull. Soc. Chim. Fr.* **1973**, *7–8*, 2472.
6. The structure of **2** was deduced from the following spectroscopic data and from C-H COSY and HMBC NMR experiments. (−)-**2**: white solid, mp 75.5–78.4°C (sublim.); $[\alpha]_D^{23}$ −41.4 (*c* 0.9, alc.); ν_{max} (KBr)/cm^{-1} 3394, 2938, 2875, 1654, 1450, 1386, 1370, 1020, 873; δ_H (400 MHz, $CDCl_3$) 0.95 (s, 3H), 1.00 (s, 3H), 1.26 (m, 2H), 1.56 (br. s, 1H), 1.70 (br. t, J=4.3 Hz, 1H), 1.72–1.88 (m, 2H), 1.94 (br. d, J=16.3 Hz, 1H), 2.47 (br. d, J=16.3 Hz, 1H), 3.82 (AB, J_{AB}=11.7 Hz, 2H), 4.80 (br. t, J=2.0 Hz, 1H), 4.85 (br. t, J=2.0 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 19.47 (q), 21.09 (q), 27.63 (t), 31.18 (t), 37.19 (t), 45.80 (d), 47.54 (s), 56.27 (s), 62.26 (t), 102.59 (t), 156.08 (s); *m*/*z* (GC/MS, EI 70 eV, % rel.) 166(8), 148(28), 135(81), 123(59), 105(82), 93(100), 81(77), 67(60), 55(33), 41(80); *m*/*z* (GC/MS, CI isobutane, % rel.) 167(27), 149(100), 135(2), 121(16), 107(23).
7. Fieser, L. F.; Fieser, M. *Reagents for Organic Chemistry*; John Wiley & Sons: New York, 1967; Vol. 1, p. 11.
8. Preparative details (Table 1, entry 12): a room temperature cooled mixture of DMSO (40 mL) and 85% H_3PO_4 (20 mL) was added to epoxide **4** (2.496 g, 15 mmol). After stirring for 30 min at rt, GC analysis of an aliquot showed the complete disappearance of epoxide **4**. 50% aq. NaOH (60 mL) solution was then added. The resulting white suspension was diluted with water (200 mL), filtered and the filtrate extracted with pentane (3×100 mL). The residue was dissolved in water (150 mL) and extracted with pentane (3×50 mL). The combined organic layers were washed with brine (2×100 mL), dried over $MgSO_4$ and the solvent was removed in vacuo to afford a white solid (2.043 g). Liquid chromatography on silica gel (cyclohexane:ethyl acetate, 96:4) gave two fractions: aldehydes **5** (0.200 g, 8% yield) and unseparated isomeric alcohols **2** and **7** (1.622 g, 65% combined yield, ratio of **2**:**7**=92:8).
9. (+)-Fenchone: $[\alpha]_D^{16}$=+69.5 (alc.): Günther, E. *The essential Oils*; Van Nostrand: New York, 1948; Vol. II, p. 420.