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A novel enantiospecific route to 10-hydroxyfenchone: a convenient intermediate for C(10)-*O*-substituted fenchones

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Abstract—A novel, highly efficient enantiospecific preparation of 10-hydroxyfenchone from commercially available fenchone is described. The three-step synthetic route is based on two consecutive Wagner–Meerwein rearrangements of the fenchone skeleton, taking place with a high overall yield. This straightforward access to optically active 10-hydroxyfenchone, together with the scope for further functionalisation of the hydroxyl group, makes 10-hydroxyfenchone a convenient key intermediate to other optically active C(10)-*O*-substituted fenchones, which are analogues of well-known C(10)-*O*-substituted camphor-derived chiral sources.

Among the great variety of chiral sources derived from camphor **1a** or fenchone **1b**,[1] C(10)-*O*-substituted camphors have been widely used as valuable chiral auxiliaries (e.g. amino ether **2a**, hydroxy ether **3a** or oxazinone **4a**) in several asymmetric transformations (Fig. 1).[2]

Nevertheless, despite the interesting complementarities existing between camphor- and fenchone-derived chiral sources (topological differences which can be reflected in different abilities of chirality transfer),[3] corresponding C(10)-*O*-substituted fenchone derivatives such as **2b**–**4b** have been neither described nor investigated. This is due to the fact that C(10)-*O*-substituted camphors are invariably obtained from commercially available enantiopure ketopinic acid **5a**, whereas the corresponding key starting fenchone-derived acid **5b** is not commercially available.[4]

In addition to ketopinic acid, enantiopure 10-hydroxycamphor **6a** has recently been described by us as a new convenient intermediate to C(10)-*O*-substituted camphors.[5] In this sense, 10-hydroxyfenchone **6b** would be the key starting intermediate to C(10)-*O*-substituted fenchones.

Unfortunately, 10-hydroxyfenchone **6b** is prepared from fenchone following a six-step route with low overall yield.[6] With this is mind, the establishment of an efficient enantiospecific route to **6b** is of a great interest, because it would allow a more straightforward access to C(10)-*O*-substituted fenchone-derived chiral sources.

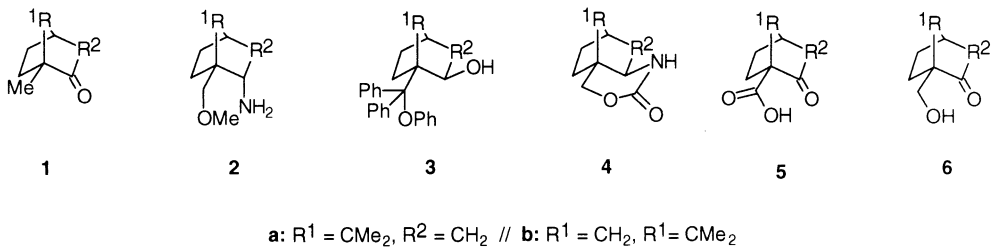

Figure 1. Some selected C(10)-*O*-substituted camphors (**a**) and corresponding fenchone derivatives (**b**).

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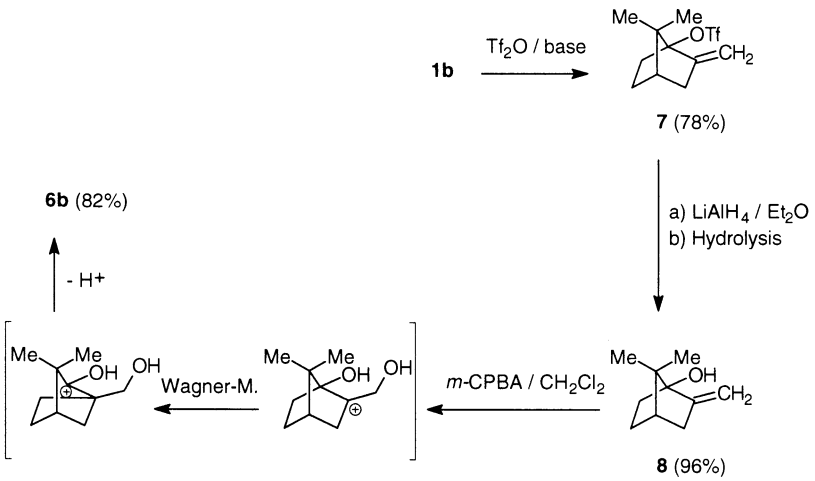

Scheme 1. Novel enantiospecific preparation of 10-hydroxyfenchone **6b**.

In this communication, we describe the first efficient enantiospecific synthesis of the valuable chiral intermediate (1*R*)-hydroxyfenchone **6b** from commercial (1*R*)-fenchone **1b** as described in Scheme 1.

The key intermediate of our synthetic route is 2-methylenenorbornan-1-ol **8** (obtained enantiospecifically from (1*R*)-fenchone via triflate **7**),[7] which, upon treatment with *m*-CPBA[8] undegoes a regio- and enantiospecific tandem carbon–carbon double bond addition-Wagner–Meerwein rearrangement to yield the desired (1*R*)-10-hydroxyfenchone **6b** (Scheme 1).[9]

In summary, a highly efficient enantiospecific preparation of 10-hydroxyfenchone from readily available commercial fenchone has been described. Only three easy individual steps are required and the overall yield is high. Mechanistically, the synthetic procedure takes place with two consecutive enantiospecific Wagner–Meerwein rearrangements of the fenchone skeleton. The herein described highly efficient preparation of 10-hydroxyfenchone **6b** will allow the facile preparation of interesting C(10)-*O*-substituted fenchone-derived chiral auxiliaries, which are interesting analogues of well known C(10)-*O*-substituted camphor-derived chiral auxiliaries.

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8. A solution of alcohol **8** and *m*-CPBA (57–86% purity) in CH_2Cl_2 was stirred at room temperature for 24 h. After standard work up (+)-**6b** was obtained as a colorless liquid (82% yield). $[\alpha]_D^{20}$ +46 (0.2, CH_2Cl_2), $[\alpha]_D^{20}$ +13.7 (0.2, EtOH), e.e. 82% (by comparison of the obtained specific rotation with the measured one for enantiopure 10-hydroxyfenchone; see next reference). IR, ^1H and ^{13}C NMR spectra were identical to those reported earlier (Ref. 6 and Mizayawa, M.; Kameoka, H. *Chem. Express* **1988**, *3*, 503).
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