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First access to enantiopure C(7)-substituted fenchones: new norbornane-based chiral materials from the chiral pool

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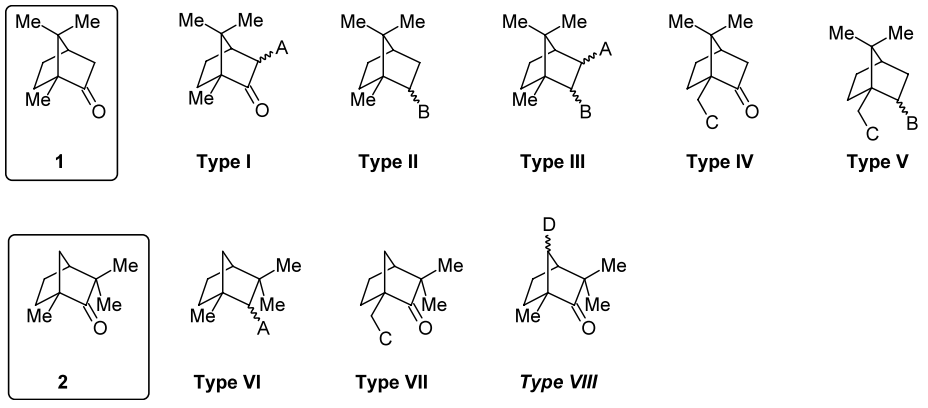
Abstract—A valuable route for the preparation of enantiopure C(7)-*anti*-substituted fenchones, a new interesting type of the C(7)-substituted-norbornane-based chiral-sources, has been established. The procedure takes place diastereoselectively in just three easy individual synthetic steps starting from readily available fenchone. The established route constitutes a model procedure for the preparation of other interesting C(7)-substituted fenchone-based chirality transfers [e.g. C(2)–C(7)-bidentate norbornane-based ligands] from the chiral pool. © 2003 Elsevier Science Ltd. All rights reserved.

Most of the plethora of norbornane-based chirality transfers (key intermediates, reagents, auxiliaries, ligands, catalysts and resolving agents) derived from the well-known natural chiral sources (+)-(1*R*)-camphor **1** and (−)-(1*R*)-fenchone **2** can be included in one of the substitution-pattern types I–VII shown in Scheme 1.[1] This is due to the facility to functionalize in a highly stereocontrolled form the C(2)-camphor or -fenchone positions (carbonyl-group chemistry), the C(3)-camphor position (camphor–enolate chemistry) and the C(10)-camphor or -fenchone positions (2-norbornyl-cation-rearrangement chemistry).[2]

Additionally, some C(7)-substituted norbornanes have been also described as valuable chirality intermediates, such as chiral key intermediates for the synthesis of high-value molecules (e.g. carboxylic acid **3** in the preparation of methyl epijasmonate and *ent*-multifidene, mesylate **4** in the preparation of pentacyclitols, or fluoride **5** in the preparation of 6′-fluorocarbocyclic



Scheme 1. Selected types of non-racemic camphor and fenchone derivatives.

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nucleosides), as well as potentially interesting conformationally-restricted bidentate chiral ligands, e.g. diol **6** for some catalytic asymmetric reactions mediated by transition metals (Fig. 1).[3]

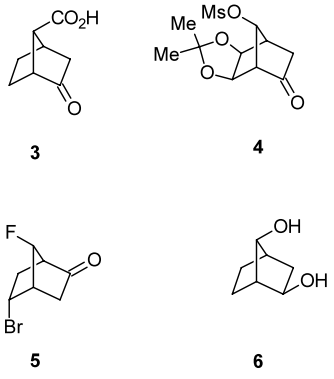


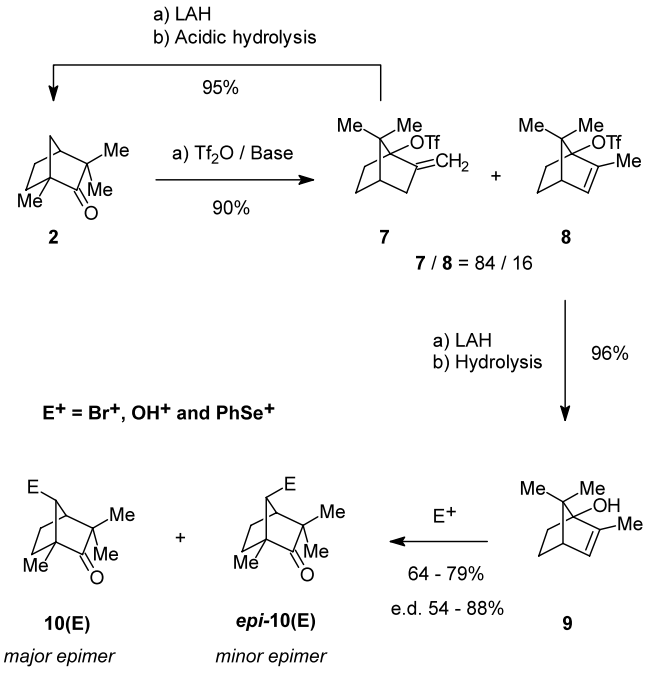
Figure 1. Some selected C(7)-substituted norbornane-based chirality transfers.

Unfortunately, most of the described enantiopure C(7)-substituted norbornanes have been prepared using non-enantioselective methods (generally involving Diels–Alder reactions), which makes necessary a subsequent resolution step.[4] On the other hand, transfunctionalization of the C(7)-norbornane position by means of a S_N2 displacement is very difficult due to two main factors:[5] (a) the small angle C(1)–C(7)–(C4) (near 93°), which makes the formation of the corresponding trigonal–bipyramid transition state difficult and, (b) the steric shielding to the nucleophile-reagent attack exerted by the C(2)-*exo* and C(3)-*exo*, or C(5)-*exo*- and C(6)-*exo*-, groups (even when such groups are hydrogen).[5]

In relation to all the above, and continuing with our ongoing research into the use of stereocontrolled Wagner–Meerwein rearrangements of 1-hydroxynorborn-2-yl carbocations for the preparation of enantiopure camphor- and fenchone-derived chirality-transfer agents,[6] we have now established a valuable procedure for the easy preparation of enantiopure C(7)-*anti*-substituted fenchones **10(E)** from enantiopure fenchone **2**, as described in Scheme 2.[7]

The key intermediate of our synthetic route is norbornenol **9**, which was straightforwardly prepared from triflate precursor **8** by LAH treatment (Scheme 2).[7,8] On the other hand, triflate precursor **8** was obtained, together with isomer **7**, from commercial (−)-(1*R*)-fenchone by a standard procedure described previously by us (Scheme 2).[7,9] Both triflates can be easily separated by elution chromatography.[10]

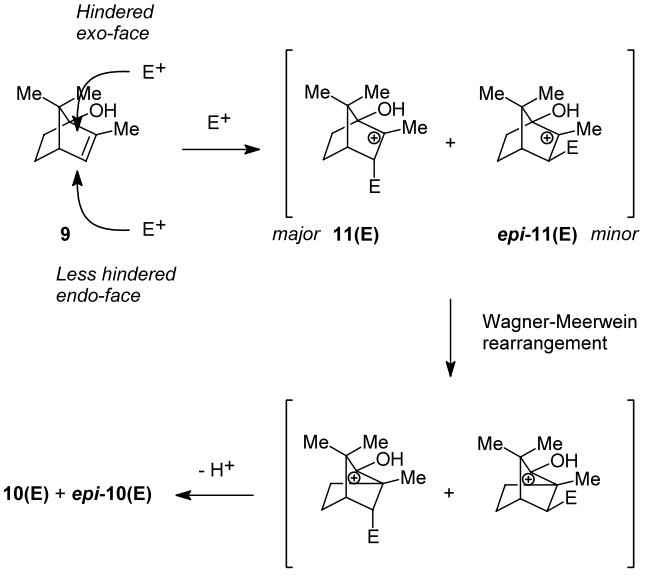
Treatment of **9** with different commercial electrophilic reagents (E^+),[7,11] such as NBS, *m*-chloroperoxibenzoic acid (*m*-CPBA) and benzeneselenylchloride, yields the corresponding C(7)-substituted fenchones **10(E)**/***epi*-10(E)** (E = Br, OH and SePh, respectively) with good yields (76% for E = Br, 64% for E = OH, and 79% for E = PhSe) and good-to-high diastereomeric excesses (56% for E = Br, 54% for E = OH, and 88% for E = PhSe) (Scheme 2).



Scheme 2. Diastereoselective fenchone-based route to optically active C(7)-substituted fenchones.

The overall efficiency of the described synthetic route can be improved by transforming triflate **7** into starting fenchone by simple LAH treatment (formation of corresponding alcohol), and subsequent hydrolysis in acidic media (enantiospecific Wagner–Meerwein rearrangement).[12]

Diastereoselective formation of **10(E)** can be explained according to the indicated in Scheme 3. Thus, regio- and stereoselective addition of the corresponding electrophile (E^+) to the C–C double bond of **9** gives place to the



Scheme 3. Diastereoselective formation of **10(E)** from **9**.

generation of the epimeric 2-norbornyl carbocations **11(E)** and ***epi*-11(E)**. These cations must then undergo a favored [C(1)-hydroxy group] enantiospecific Wagner–Meerwein rearrangement,[6] to generate, after proton elimination, the corresponding final C(7)-substituted fenchones **10(E)** and ***epi*-10(E)**.

In summary, a valuable route to a new type of fenchone-derived chiral substrates, the C(7)-substituted-fenchone ones (see Type VIII in Scheme 1), has been established. The procedure has been exemplified by the synthesis of three new 7-substituted fenchones (7-bromo-, 7-hydroxy- and 7-phenylselanyl). The procedure takes place diastereospecifically in three easy individual steps, the key step is a stereocontrolled tandem electrophilic C–C double-bond addition–Wagner–Meerwein rearrangement into key intermediate 2,7,7-trimethylnorbonen-1-ol **9**, to generate preferentially the C(7)-*anti*-substituted epimer. The described route constitutes a model procedure for the preparation of other interesting C(7)-substituted-norbornane-based chirality transfers.

Acknowledgements

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4. For an example, see kinetic resolution of racemic **5** in Ref. 3g.
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7. Since the starting commercial (–)-fenchone **2** has an ee of 82% all products enantiospecifically obtained from it must possess the same enantiomeric excess. This fact has been previously tested by us (García Martínez, A., Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2001**, *12*, 3325).
8. Alcohol **9** was prepared from triflate **8** according to a general procedure previously described by us: García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Ruano Franco, C.; Soto Salvador, J.; Subramanian, L. R.; Hanack, M. *Synthesis* **1987**, 321. **9**: White solid. Mp 41–42°C. $[\alpha]_D^{20}$ –2.2 (4.3, CH_2Cl_2). IR, ^1H and ^{13}C NMR and HRMS agree with the structure.
9. On the enantiospecific reaction of (–)-fenchone with triflic anhydride see Ref. 6. Elution-chromatography separation yields minority triflate **8** in 12% yield as a colorless oil.
10. Silica gel/hexane.
11. A solution of alcohol **9** in CH_2Cl_2 was treated with the corresponding electrophile reagent (NBS, 50% purity *m*-CPBA or benzeneselenyl chloride) at room temperature. After standard work-up and purification by elution chromatography [silica gel; hexane/CH_2Cl_2 4:1 for **10(Br)** and **10(PhSe)**, and hexane/Et_2O 7:1 for **10(OH)**] pure corresponding C(7)-*anti*-substituted fenchone **10(E)** was obtained. **10(Br)**: White solid. Mp 45–46°C. $[\alpha]_D^{20}$ +163.1 (2.2, $CHCl_3$). **10(OH)**: Colorless oil. $[\alpha]_D^{20}$ –14.7 (1.5, $CHCl_3$). **10(PhSe)**: Pale-yellow liquid. $[\alpha]_D^{20}$ +86.3 (1.0, $CHCl_3$). Corresponding IR, ^1H and ^{13}C NMR and HRMS agree with the structures. The stereochemistry was confirmed by NOE experiments.
12. About a related tandem proton addition–Wagner–Meerwein rearrangement, see Ref. 6.