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First efficient preparation of enantiopure 10-bromofenchone: the key intermediate to C10-substituted fenchone-derived chiral sources

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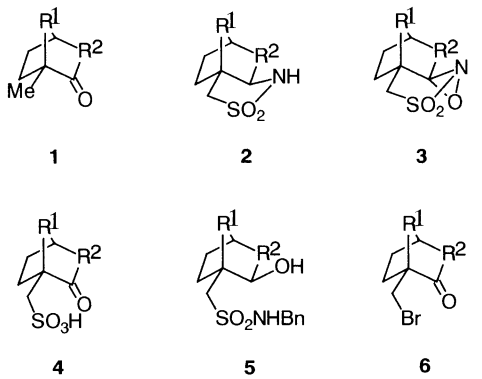
Abstract—The first efficient preparation of enantiopure 10-bromofenchone from commercially available fenchone is described. The synthetic procedure is based on two consecutive Wagner–Meerwein rearrangements of the fenchone skeleton, taking place straightforwardly in only three individual steps with a high overall yield. The ability of the bromine atom to be substituted by other functional groups makes 10-bromofenchone a key intermediate for the preparation of interesting C10-substituted fenchone-derived chiral sources, which are topologically different and analogous to well-known C10-substituted camphor-derived chiral tools. © 2001 Elsevier Science Ltd. All rights reserved.

Enantiopure derivatives of camphor **1a** and fenchone **1b** have been widely used as chiral sources.[1] Generally, the different position of the *gem*-dimethyl group in both kinds of derivatives (located at C7 for camphor derivatives and at C3 for fenchone ones, Fig. 1) confers a topological difference to both structural types,[2,3] which can be reflected in a different ability for the chirality transfer (reaction rates and optical purities) when such partners are compared as chiral catalysts, auxiliaries or reagents on an asymmetrically determined transformation.[3] In this sense, camphor and fenchone derivatives could be complementary chiral sources, which makes the study of the behavior of both structural types (C3- or C7-dimethyl-substituted) in a specific asymmetric application interesting.



1 **2** **3**

4 **5** **6**

a: $R^1 = CMe_2$, $R^2 = CH_2$; **b:** $R^1 = CH_2$, $R^2 = CMe_2$

Figure 1. Some selected C10-substituted camphors (**a**) and corresponding fenchone derivatives (**b**).

Among the great variety of camphor- and fenchone-derived chiral sources, C10-substituted camphor derivatives must be outlined due to their special significance as chiral auxiliaries (e.g. Oppolzer's sultame **2a**), chiral reagents (e.g. Davis' oxaziridine **3a**), chiral resolving agents (e.g. 10-camphorsulfonic acid **4a**), chiral catalysts (e.g. sulfonamide **5a**), as well as chiral synthetic intermediates in the preparation of high value molecules (e.g. in the total synthesis of anticancer taxol) (Fig. 1).[1a,4] Nevertheless, corresponding C10-substituted fenchone derivatives (e.g. **2b**–**5b**) have neither been widely described nor probed.[5] This is due to the fact that most of the C10-substituted camphor derivatives are obtained from 10-camphorsulfonic acid **4a** (the first obtained C10-substituted camphor),[4,6] whereas the corresponding key starting 10-fenchonesulfonic acid is not commercially available.[5a]

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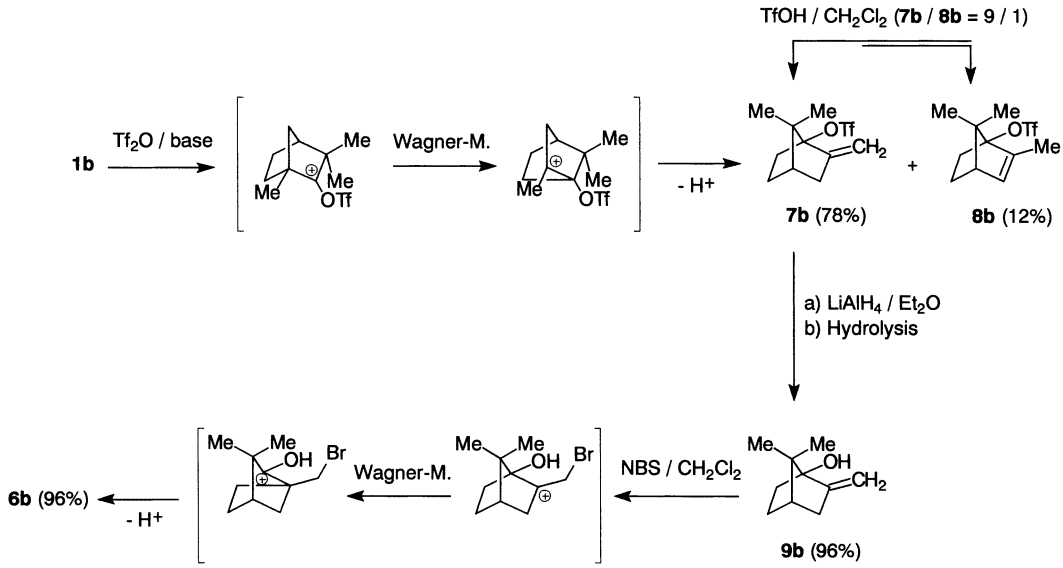

Scheme 1. Novel enantiospecific preparation of 10-bromofenchone **6b**.

On the other hand, a key intermediate for the preparation of C10-substituted camphors is 10-bromocamphor **6a** (also obtained until recently[7] from **4a**), due to the fact that the halogen atom can be replaced by other functional groups via a nucleophilic-substitution reaction (e.g. C10-Br→C10-O,[6a] C10-Br→C10-Se,[6i] C10-I→C10-Te,[6j] C10-Br→C10-P,[6h] or C10-I→C10-P[6l]). Unfortunately, the analogous key intermediate 10-bromofenchone **6b** is obtained in very low yield (11%) according to the procedure described by Tarbell and Loveless in 1958.[5b] With this in mind, the establishment of an efficient synthetic route to enantiopure 10-bromofenchone **6b** is of a great interest, because it allows the preparation of other valuable enantiopure C10-substituted fenchones (by bromine substitution), which are difficult to obtain by other routes.[5]

In this communication, we describe the efficient preparation of interesting key enantiopure intermediate (1*S*)-10-bromofenchone **6b** from commercially available (1*R*)-fenchone **1b** following a route previously established by us for the preparation of **6a**.[7] Only three easy synthetic steps, which take place under mild reaction conditions and with excellent yields, are required (Scheme 1).

The first step consists of the reaction of **1b** with triflic anhydride (Tf_2O) to yield a mixture of triflates **7b** and **8b**.[8] After separation,[9] triflate **7b** is reduced with lithium aluminum hydride to give the corresponding 2-methylenenorbornan-1-ol **9b**.[10] Finally, treatment of alcohol **9b** with *N*-bromosuccinimide (NBS) furnishes the desired (1*S*)-10-bromofenchone **6b**, by regio- and enantiospecific tandem electrophilic carbon–carbon double bond addition–Wagner-Meerwein rearrangement.[11] Triflate **8b** can be isomerized to **7b** by proton-catalyzed equilibration, which improves the overall yield of the described procedure.[12]

In conclusion, the first highly efficient preparation of enantiopure 10-bromofenchone **6b** has been described. The synthetic procedure is based on two consecutive Wagner–Meerwein rearrangements of the fenchone skeleton. The described preparation takes place enantiospecifically in only three steps starting from commercially available (1*R*)-fenchone **1b** with an overall yield of 78%. The described access to **6b** will allow the efficient preparation of C10-substituted fenchone-derived chiral inducers, which are interesting and analogous to well-known C10-substituted camphor-derived chiral inducers.

Acknowledgements

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8. For the enantiospecific synthesis of triflate **7b**, we have used a variant of the standard procedure previously described by us (García Martínez, A.; Teso Vilar, E.; Osío Barcina, J.; Rodríguez Herrero, M. E.; de la Moya Cerero, S.; Hanack, M.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1993**, *4*, 2333), consisting of the use of triisobutylamine as a non-nucleophilic base instead of *N*,*N*-diisobutyl-2,4-dimethylpent-3-ylamine, which is no longer commercial.
9. Triflates **7b** and **8b** can be easily separated by elution chromatography (silica gel/pentane).
10. Alcohol **9b** is obtained from triflate **7b** according to the methodology described in: García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Ruano Franco, C.; Soto Salvador, J.; Subramanian, L. R.; Hanack, M. *Synthesis* **1987**, 321. The structure of **9b** was confirmed by ^{1}H and ^{13}C NMR, IR, and MS.
11. A solution of alcohol **9b** and *N*-bromosuccinimide in dry CH_2Cl_2 is stirred at room temperature for 24 h. After usual work-up, **6b** is obtained as a colorless liquid (96% yield). $[\alpha]_D^{20}$ −3 (0.31, CH_2Cl_2). IR (film) ν 1740, 1464, 1364 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.71 (d, $J=10.7$ Hz, 1H), 3.51 (d, $J=10.7$ Hz, 1H), 2.19 (br s, 1H), 2.08–1.98 (dm, $J=10.5$ Hz, 1H), 1.94–1.70 (several m, 3H), 1.70 (dd, $J=10.5$ Hz, $J=1.9$ Hz, 1H), 1.55–1.22 (m, 1H), 1.07 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 219.4, 59.1, 48.3, 44.8, 39.2, 32.3, 28.9, 25.2, 22.9, 21.5 ppm. MS m/z 232 [$M^{+\bullet}$ (^{81}Br), 3], 230 [$M^{+\bullet}$ (^{79}Br), 3], 151 ($M^{+\bullet}$−Br, 10), 123 (100).
12. Over a solution of triflate **8b** in CH_2Cl_2, at −15°C, was slowly added 50% mol equiv. of triflic acid. The solution was stirred for 15 min and quenched with saturated sodium bicarbonate solution. After usual work-up, a mixture of **7b**/**8b** (9/1) was obtained in 98% yield.