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A new highly efficient synthetic route to enantiopure 10-bromocamphor

Beatriz Lora Maroto,[a] Santiago de la Moya Cerero,[a,*] Antonio García Martínez,[a,*] Amelia García Fraile[b] and Enrique Teso Vilar[b]

[a]*Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Ciudad Universitaria, 28040 Madrid, Spain*

[b]*Departamento de Química Orgánica y Biología, Facultad de Ciencias, Universidad Nacional de Educación a Distancia (UNED), Senda del Rey 9, 28040 Madrid, Spain*

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Abstract

A new enantiospecific synthetic route to the interesting chiral synthetic intermediate 10-bromocamphor starting from readily available camphor is described. The procedure takes place straightforwardly in only three synthetic steps with high overall yield. Mechanistically, two interesting enantiospecific Wagner–Meerwein rearrangements involving 2-norbornyl carbocations take place during the process.

Enantiopure C10-substituted camphor derivatives have been widely used as chiral starting materials in asymmetric synthesis,[1] as well as interesting chiral synthetic intermediates in the preparation of natural products.[2] Unfortunately, most of these derivatives have, as a common chemical characteristic, the presence of a sulfur atom attached to the C10 position (C10–S).[1] This common presence of sulfur at C10 is due to the fact that most of the synthetic routes for the preparation of C10-substituted camphors start from 10-camphorsulfonic acid (the first C10-substituted camphor derivative obtained),[3] or the now commercially available 10-camphorsulfonyl chloride.[1–3]

Nevertheless, nowadays, several enantiopure camphor derivatives having a C10-substitution different than the common C10–S, such as C10–O (e.g. **1**), C10–N (e.g. **2**), C10–halogen (e.g. **3**), C10–P (e.g. **4**) or C10–Se (e.g. **5**) (Fig. 1), have also been described as very interesting sources of chirality.[4] In this sense, 10-bromocamphor **3** is a very convenient and a key synthetic precursor to C10-substituted camphor derivatives, since the bromine atom can be replaced via a nucleophilic substitution reaction (e.g. C10–Br→C10–O,[4a] C10–Br→C10–Se,[4i] or C10–Br→C10–P[4j]). Unfortunately, up to now 10-bromocamphor **3** has only been prepared enantiospecifically from 10-camphorsulfonic acid in a very low overall yield (20%), following a procedure described by

* Corresponding authors. E-mail: santmoya@eucmax.sim.ucm.es

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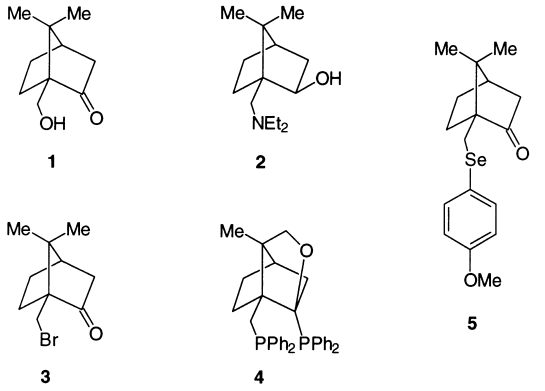
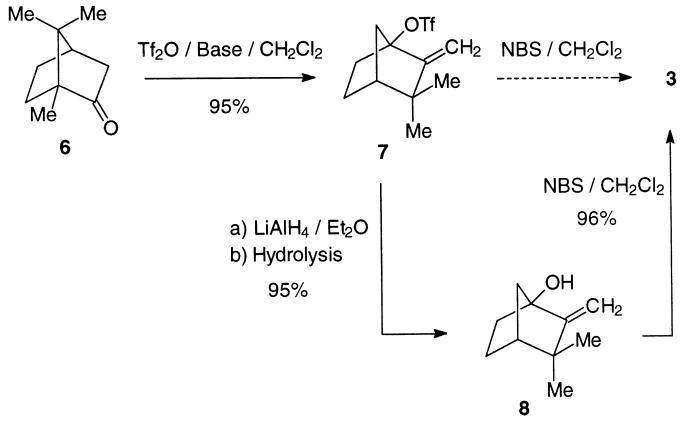


Figure 1. Some selected C10-substituted camphors with a C10-substitution different than C10–S

Dallacker et al. in 1961.[4a] This renders synthetic routes using 10-bromocamphor as starting material unattractive.[4a,i,j]

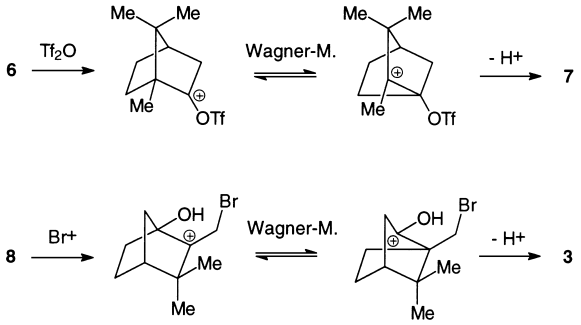
In this communication, we describe a new highly efficient synthetic route to (1*R*)-10-bromocamphor **3** starting from natural (1*R*)-camphor **6**. Only three simple synthetic steps, which take place under mild reaction conditions and with excellent yields, are required (Scheme 1).

The first step is the preparation of (1*R*)-3,3-dimethyl-2-methylenenorborn-1-yl triflate **7** from commercial (1*R*)-camphor **6** by reaction with triflic anhydride.[5] Triflate **7** is subsequently reduced with lithium aluminum hydride to give the corresponding 2-methylenenorbornan-1-ol **8**.[6] Finally, the treatment of alcohol **8** with *N*-bromosuccimimide (NBS) yields the desired (1*R*)-10-bromocamphor **3**.[7] Obtaining synthetic intermediate **8** is necessary since the 2-methylenenorborn-1-yl triflate **7** does not react with NBS under the same conditions as alcohol **8**.



Scheme 1. New highly efficient enantiospecific preparation of 10-bromocamphor **3**

The key steps of the above-described synthetic procedure are: (1) the enantiospecific preparation of triflate **7** by Wagner–Meerwein rearrangement of **6** by reaction with triflic anhydride; and (2) a second enantiospecific Wagner–Meerwein rearrangement of the 2-methylenenorbornan-1-ol **8** by carbon–carbon double bond addition of electrophilic bromine (Br^+), under a straightforward NBS treatment (Scheme 2).



Scheme 2. Wagner–Meerwein rearrangements involved in the described preparation of 10-bromocamphor **3**

In conclusion, a new enantiospecific route to the interesting chiral source 10-bromocamphor **3** has been described. 10-Bromocamphor **3** is now obtained in only three steps starting from commercially available (1*R*)-camphor **6**, the complete process having an overall yield of 87%. This straightforward preparation of **3** opens the way to the efficient preparation of other important enantiopure C10-substituted camphor derivatives.

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7. A solution of alcohol **8** and *N*-bromosuccinimide in dry CH_2Cl_2 is stirred at room temperature for 24 h. After the usual work-up, **3** is obtained as a white solid (95% yield). Pf. 69–70°C. $[\alpha]_D^{20}$ +14.6 (0.20, CH_2Cl_2). The structure was confirmed by ^1H NMR, ^{13}C NMR, IR, MS and HRMS.