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TETRAHEDRON: *ASYMMETRY*

A new straightforward preparation of enantiopure 10-hydroxycamphor

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Abstract

The enantiospecific preparation of the interesting chiral source 10-hydroxycamphor from commercially available camphor is described. The synthetic procedure takes place straightforwardly in only three synthetic steps with a high overall yield. The key step of the described route is based on the ability of a 2-methylenenorbornane intermediate to undergo an enantiospecific Wagner–Meerwein rearrangement under electrophilic treatment with *m*-CPBA. © 2000 Elsevier Science Ltd. All rights reserved.

Enantiomerically pure C10-substituted camphor derivatives have found broad application as chiral reagents, auxiliaries and catalysts in asymmetric synthesis,[1] as well as versatile chiral synthetic intermediates for the total synthesis of high-value molecules (e.g. natural products).[2] Most of the C10-substituted camphor derivatives present a sulfur atom attached to the C10 position (C10-S),[1] because almost all of the synthetic routes described for the preparation of this kind of compound use 10-camphorsulfonic acid (the first C10-substituted camphor derivative obtained),[3] or 10-camphorsulfonyl chloride, as starting material.[1–3]

Nevertheless, some modern enantiopure camphors with a C10-substitution different from the common C10-S, such as C10-O, C10-N, C10-halogen, C10-P or C10-Se, have been prepared and tested as valuable chiral sources.[4] Among them, C10-O derivatives (e.g. **1**–**4** in Fig. 1) must be specially mentioned due to their application as chiral inducers (auxiliaries and reagents) in several interesting asymmetric transformations.[4b,4d–f]

In this sense, 10-hydroxycamphor **5** (Fig. 1) is a key intermediate (together with ketopinic acid) to C10-O-substituted camphor derivatives.[4a–g] Unfortunately, 10-hydroxycamphor is prepared from 10-camphorsulfonic acid in five steps with a low overall yield (12%), according to the

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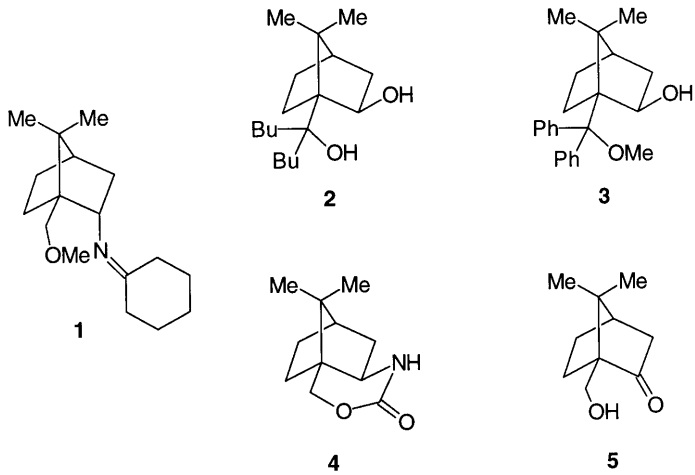
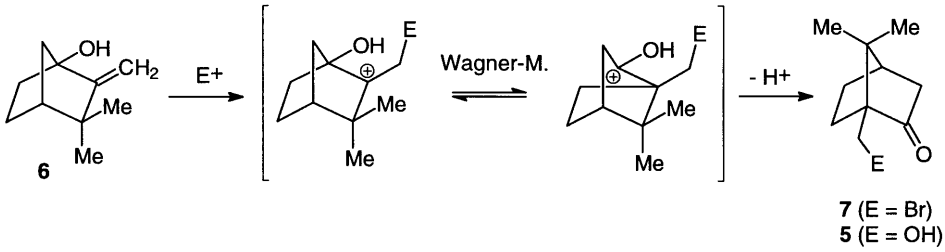


Figure 1. Some interesting C10-O-substituted camphors

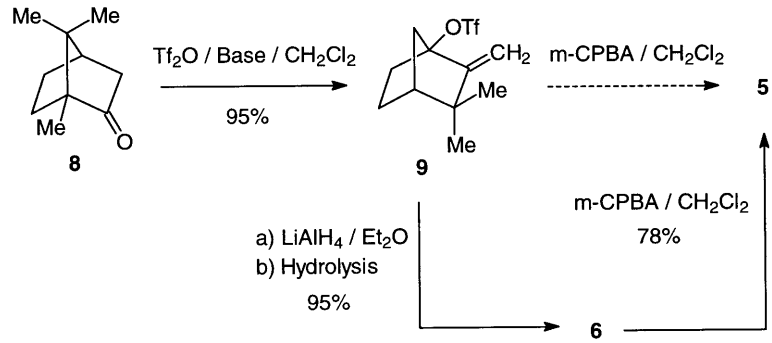
synthetic route described by Dallacker et al. in 1961.[4a] Due to this limitation, until now, 10-hydroxycamphor **5** has been used very rarely (in comparison to ketopinic acid) as starting precursor of other C10-O-substituted camphor derivatives.[4a–g]

Recently, we have described that reaction of enantiopure 3,3-dimethyl-2-methylenenorbornan-1-ol **6** with *N*-bromosuccinimide (NBS) as electrophilic reagent yields 10-bromocamphor **7** enantiospecifically.[5] The process takes place through a regio- and enantiospecific tandem electrophilic carbon–carbon double bond addition—Wagner–Meerwein rearrangement on the 2-methylenenorbornane **6** (Scheme 1, $E^+ = Br^+$). On the other hand, enantiopure precursor **6** can be easily obtained from camphor **8** in two steps, in a high yield and under mild reaction conditions (see Scheme 2).[5] The use of **7** (obtained as described above) as an intermediate in the Dallacker's preparation of 10-hydroxycamphor **5** will improve the overall yield of that synthetic route (ca. 58%).[6]



Scheme 1. Tandem electrophilic carbon–carbon double bond addition—Wagner–Meerwein rearrangement of **6**

Now we have found that the treatment of (1*R*)-3,3-dimethyl-2-methylenenorbornan-1-ol **6** with *meta*-chloroperoxybenzoic acid (*m*-CPBA) as electrophile, instead of NBS, enantiospecifically yields (1*R*)-10-hydroxycamphor **5** as the only product (the corresponding expected diastereomeric epoxides of **6** were not detected) (Scheme 2). The reaction takes place in high yield (78%) under mild reaction conditions (methylene dichloride solution at room temperature).[7] Triflate intermediate **9** does not react with *m*-CPBA under the same reaction conditions as **6** does.



Scheme 2. New straightforward route to enantiopure 10-hydroxycamphor

Formation of **5** from **6** can be easily achieved according to the mechanism proposed in Scheme 1 ($E^+ = OH^+$).

In conclusion, a new enantiospecific route to the interesting chiral intermediate 10-hydroxycamphor **5**, based on the Wagner–Meerwein rearrangement of a convenient 2-methylenenorbornane, has been described. 10-Hydroxycamphor **5** is now obtained in only three synthetic steps starting from readily available enantiopure camphor **8**. The complete synthetic route has an overall yield of 70%. The availability of **5** following the procedure described will allow the straightforward synthesis of other interesting enantiopure C10-O-substituted camphor-derived chiral sources.

Acknowledgements

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6. 10-Bromocamphor is enantiospecifically obtained from camphor in three steps with 95% overall yield (see Ref. 5). 10-Hydroxycamphor is obtained from 10-bromocamphor in two steps with 61% overall yield (see Ref. 4a).
7. A solution of alcohol **6** and *meta*-chloroperoxybenzoic acid (57–86% purity) in CH_2Cl_2 was stirred at room temperature for 24 h. After usual work up, **5** was obtained as a white solid (78% yield). Mp 216–218°C. $[\alpha]_D^{20}$ +18.8 (0.17, CH_2Cl_2). The structure was confirmed by ^1H, ^{13}C NMR, IR, MS and HRMS.