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Enantiospecific Access to Various C(9),C(10)-Disubstituted Camphors: Scope and Limitations[§]

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Abstract: The valuable chiral sources C(9),C(10)-disubstituted camphors can be enantiospecifically obtained from the corresponding C(9)-substituted camphors by a general and straightforward synthetic method. This method involves the electrophilic treatment of a key 2-methylenenorbornan-1-ol intermediate, followed by a controlled tandem carbon−carbon double-bond addition−Wagner-Meerwein rearrangement of the norbornane framework. Discussion of the results presented suggests possible extensions and limitations of the methodology used. The feasibility of this method has been exemplified by the highly efficient enantiospecific preparation of several interesting C(9)-*halogen*-, C(10)-*halogen*, *O*-, *S*-, or *Se*-substituted camphors.

Derivatives of C(10)-substituted camphor **1(H/Y)** can be considered the most important family of chirality transfer agents derived from camphor.[1] The C(10)-substituted-camphor moiety can be easily recognized in a great number of very valuable chiral resolving agents [e.g., 10-camphorsulfonic acid **1(H/SO$_3$H)**],[2] chiral auxiliaries (e.g., Oppolzer's sultam **2**),[3] chiral reagents (e.g., Davis' oxaziridine **3**),[4] chiral catalysts (e.g., Yus' hydroxysulfonamide **4** for the asymmetric addition of diethylzinc to aldehydes and ketones),[5] or chiral key intermediates [e.g., 10-methylenecamphor **1(H/=CH$_2$)** in Paquette's approach to taxol)[6] (Figure 1).

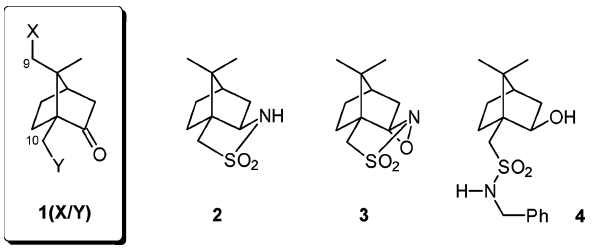

FIGURE 1. Some valuable chiral sources based on C(9)- and C(10)-substituted camphors.

In addition, enantiopure derivatives of C(9)-substituted camphor **1(X/H)** have also found application as chirality transfer agents, in this case, mainly as key chiral synthetic intermediates [e.g., 9-cyanocamphor **1(CN/H)** in the elegant syntheses of vitamins B_{12} and D developed by Stevens,[7] or 9-bromocamphor **1(Br/H)** in some total syntheses of furodisines, cannabidiols, and magnolols[8]] (Figure 1).

It can therefore be safely predicted that enantiopure derivatives of C(9),C(10)-disubstituted camphor **1(X/Y)** would be a new family of camphor-based chiral sources which combines the structural characteristics of the C(9)- and C(10)-substituted camphors (Figure 1). This family should find valuable applications in stereoselective and asymmetric syntheses. Enantiopure **1(Br/I)**, for example, would be a valuable new intermediate with the ability to react selectively with nucleophiles, initially at the more reactive C(10)-*I*-substituted position and then at the C(9)-*Br*-substituted one. Unfortunately, preparations of such derivatives are not easy (see below).[9]

Our efforts in Wagner-Meerwein rearrangements as synthetic tools in the preparation of bridgehead intermediates,[10] and particularly in the preparation of C(10)-substituted camphors and fenchones,[11] led us to report a new and straightforward synthetic route to enantiopure mixed 9,10-dihalocamphors.[12] This route (Scheme 1) includes the following: (1) an initial base-controlled triflic-anhydride-promoted Wagner-Meerwein rearrangement of a readily accessible C(9)-substituted camphor

[§] In memory of Dr. del Amo Aguado, our dear colleague and friend, a tragic victim of the terrorist bombing in Madrid, March 11, 2004.

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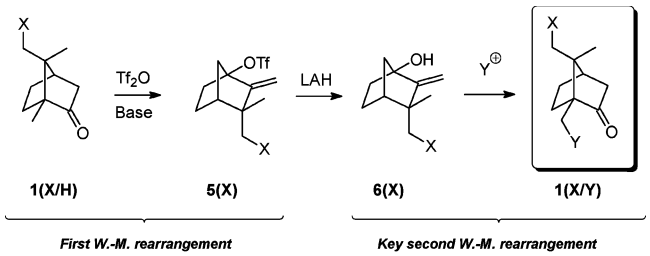
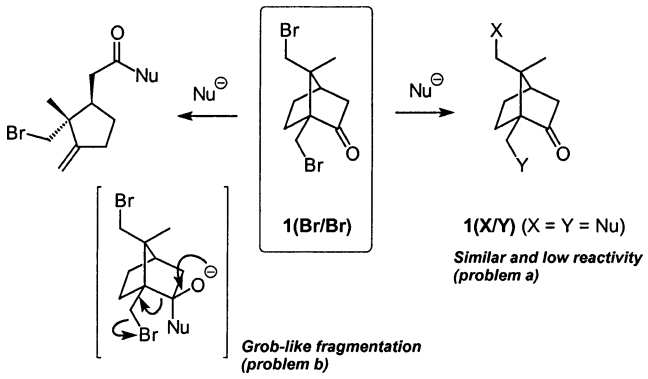
SCHEME 1. Synthetic Route to C(9),C(10)-Substituted Camphors 1(X/Y)



SCHEME 2. Synthetic Problems in Preparing 1(X/Y) from 1(Br/Br)



l(X/H) (X = halogen) to the corresponding bridgehead 2-methylenenorborn-1-yl triflate **5(X)**,[12] followed by (2) a second electrophile-promoted (*N*-halosuccinimide) Wagner-Meerwein rearrangement of the triflate-derived methylenenorbornanol **6(X)** to yield the corresponding C(9),C(10)-disubstituted camphor **1(X/Y)** (X and Y are halogens in such previously communicated cases).[12]

In this paper we provide insight into the scope and limitations of this synthetic method, extending it to other derivatives, including some interesting new disubstituted C(9)-*halogen*, C(10)-*O*, *S*, or *Se* camphor derivatives.

Although enantiopure C(10)- and C(9)-substituted camphors are now accessible,[1b,9,11h] the preparation of enantiopure C(9),C(10)-disubstituted camphors presents some serious difficulties.[9,13] In fact, the only readily accessible one, 9,10-dibromocamphor **1(Br/Br)**, has been used to date as the only disposable enantiopure synthetic intermediate to other C(9),C(10)-disubstituted camphors (via nucleophilic substitution of the bromine groups).[9] This identically C(9),C(10)-disubstituted camphor (X = Y = Br) was prepared by an interesting selective camphor-bromination technique developed by Money et al. during the late 70's.[13] Unfortunately, this route to **1(Br/Br)** takes place with a very low overall yield (31% from 3-*endo*-9-dibromocamphor),[13b,14] and it cannot be extended to other halogens. In addition, there are two serious problems in the conversion of **1(Br/Br)** to other C(9),C(10)-disubstituted camphors **1(X/Y)**: (a) the similar and low reactivity of both bromomethyl groups (actually neopentyl-like bromides)[9c] of **1(Br/Br)** toward nucleophilic substitution and (b) the possibility of a Grob-like fragmentation in the rigid β-halosubstituted ketone **1(Br/Br)** under nucleophilic treatment.[15] The latter problem is resolved by protecting the carbonyl group[9c] (Scheme 2).

Problem a (Scheme 2) could be avoided by employing the double Wagner-Meerwein strategy in Scheme 1 for the preparation of 9,10-dihalocamphor with different halogens at the neopentyl-like positions. This strategy, however, does not circumvent the Grob-like fragmentation problem.

To simplify the synthetic access to the desired various C(9),C(10)-disubstituted camphors **1(X/Y)**, we were interested in studying the scope of the electrophilic-promoted Wagner-Meerwein rearrangement of camphor-derived alcohols **6(X)** (Scheme 1) with electrophiles other than the *N*-halosuccinimides [NCS, NBS, and *N*-iodosuccinimide (NIS)] previously used.[12] The previously reported Wagner-Meerwein rearrangement of simple (non-heteroatomically substituted) camphor- and fenchone-derived 2-methylenenorbornan-1-ols with several commercial *O*-, *S*-, *Se*-, and *C*-electrophiles, such as *m*-CPBA, *p*-nitrobenzenesulfenyl chloride, benzeneselenyl chloride, and *N*,*N*-dimethylmethaniminium iodide (Eschenmoser's salt),[11h] led us to investigate the reactivity of the bromo-

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(14) Actually, the low yield in obtaining **1(Br/Br)** can be resolved by preparing it directly from the nowadays commercial intermediate 3,9,10-tribromocamphor.

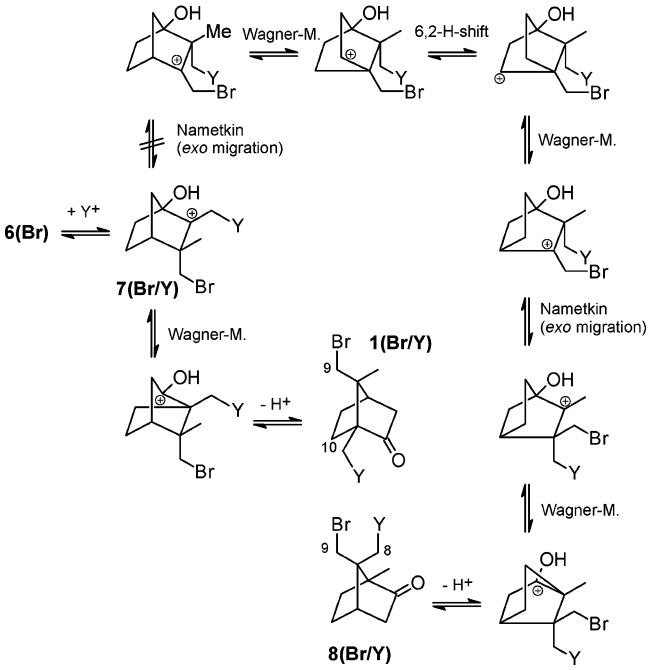
(15) As a review see: (a) Becker, K. B.; Grob., C. A. In *The Chemistry of the Double-bonded Functional Groups*; Patai, A. S., Ed.; Interscience: New York, 1977; Part II Supplement. As an example, see: (b) Levitt, M. S.; Newton, R. F.; Roberts, S. M.; Willets, A. J. *J. Chem. Soc., Chem. Commun.* **1990**, *8*, 619.

TABLE 1. Electrophilic Treatment of 2-Methylenenorbornan-1-ol 6(Br): Enantiospecific Preparation of C(10)-Substituted 9-Halocamphors

entry	electrophilic reagent	additive	reaction product	yield (%)
1	NCS	none	**1(Br/Cl)**	83
2	NBS	none	**1(Br/Br)**	85
3	NIS [a]	none	**1(Br/I)**	80
4	*m*-CPBA	none	**1(Br/OH)**	75
5	*p*-NO_2-C_6H_4-SCl	none	**1(Br/*p*-NO_2-C_6H_4-S)**	78
6	*p*-NO_2-C_6H_4-SCl	ZnI_2	**1(Br/I)**	73
7	C_6H_5-SeCl	none	**1(Cl/C_6H_5-Se)**	75
8	C_6H_5-SeCl	ZnI_2	**1(I/C_6H_5-Se)**	77
9	$[CH_2{=}NMe_2]^+,I^-$	none	no reaction [b]	

[a] *N*-Iodosuccinimide. [b] In refluxing $CHCl_3$.

SCHEME 3. Possible Reaction Pathways for the Treatment of 6(Br) with Electrophiles

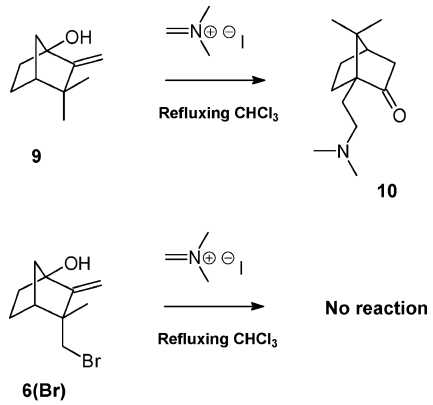


substituted camphor-derived 2-methylenenorbornan-1-ol **6(Br)** with the same electrophiles at the same reaction conditions. The results are shown in Table 1 [the previous results on the reaction with halogenating electrophiles[12] (*N*-halosuccinimides) are included for comparison].

As in the previously described case of the simple (nonheteroatomically substituted) camphor- or fenchone-derived 2-methylenenorbornan-1-ols,[11h] the initially formed 2-norbornyl-cation intermediate **7(Br/Y)** produced only the desired C(9),C(10)-disubstituted camphor **1(Br/Y)** via a subsequent Wagner-Meerwein rearrangement, and not the C(8),C(9)-disubstituted camphor **8(Br/Y)** via a Nametkin rearrangement (Scheme 3). This exquisite control of the reaction pathway can be explained due to an electronic activation for the Wagner-Meerwein rearrangement exerted by the C(1)-hydroxyl group [note the hydroxyl stabilization (+K effect) of the 2-norbornyl cation formed after Wagner-Meerwein rearrangement of **7(Br/Y)**],[16] which is more effective than a possible

(16) This effect has been previously demonstrated by us and other authors (see ref 11h and other references therein).

SCHEME 4. Different Reactivity of 9 and 6(Br) toward Eschenmoser's Salt



electronic activation for the Nametkin rearrangement exerted by the C(3)-*endo*-bromomethyl group (*β*-bromine effect).

Although **6(Br)** reacts effectively with several electrophilic reagents to yield the expected products (cf. entries 1−5 in Table 1, and Scheme 3), unexpected products are obtained in other cases (entries 6−8 in Table 1). That **6(Br)** does not react with the carbon-electrophile Eschenmoser's salt (entry 9 in Table 1) can be explained by the lower reactivity of this *C*-electrophile. In fact, we have previously reported that the reaction of 3,3-dimethyl-2-methylenenorbornan-1-ol [**6(H)**] with Eschenmoser's salt requires more rigorous reaction conditions (refluxing chloroform) than the standard reaction of the same 2-methylenenorbornan-1-ol with other electrophiles (methylene dichloride solution at room temperature).[11h] Additionally, the reactivity of the bromo-substituted 2-methylenenorbornan-1-ol **6(Br)** is lower than **9**, probably due to a destabilizing field effect exerted by the bromine atom on the electrophilic reaction (Scheme 4).

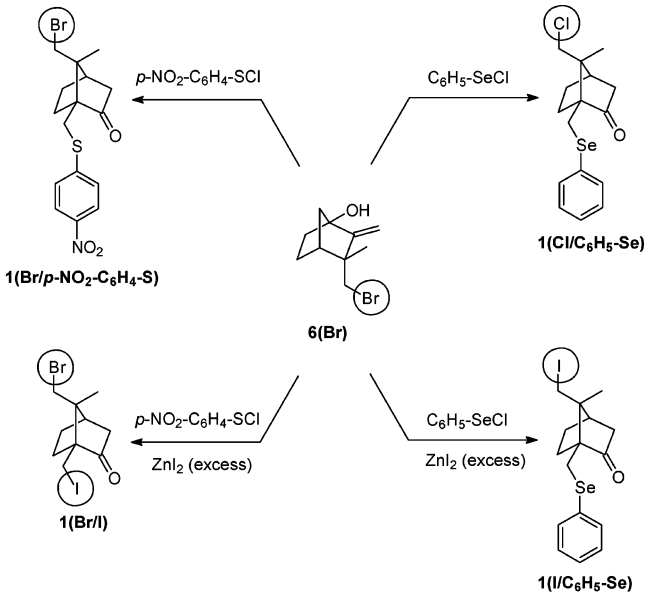
The products of the reaction of **6(Br)** with four reagent combinations (cf. entries 5−8, Table 1) reveal a striking variability (Scheme 5). All reaction pathways involve electrophilic addition−Wagner-Meerwein rearrangement. In the case of reaction 7, when compared with reaction 5, there is an additional bromine substitution to form **1(Cl/C_6H_5-Se)** instead of **1(Br/C_6H_5-Se)**. Addition of excess zinc iodide[17] to the selenylating reagent caused bromine substitution to form **1(I/C_6H_5-Se)** (entry 8, Table 1). Finally, treatment of **6(Br)** with *p*-nitrobenzenesulfenyl chloride and excess zinc iodide (entry 6**,** Table 1) produces **1(Br/I)** via a triple tandem electrophilic addition−Wagner-Meerwein rearrangement−nucleophilic substitution of the good leaving (*p*-nitrophenyl)sulfanyl group.[17,18]

Regarding reactions with the selenylating reagent (Scheme 5), bromine substitution under such mild reaction conditions is unusual for the neopentyl-like system

(17) Other iodides (e.g., sodium iodide) can be used instead of zinc iodide. The presence of water in hydroscopic sodium iodide can produce variable amounts of **1(Br/H)**, due to the hydrolysis of the electrophilic reagent and subsequent proton addition to **6(Br)** (also see ref 11h).

(18) The easy substitution of the neopentylic-like (*p*-nitrophenyl)-sufanyl group in **1(Br/*p*-NO_2-C_6H_4-S)** has been demonstrated by treatment of this sulfide with an excess of iodide (sodium iodide or zinc iodide in CH_2Cl_2 at room temperature) to generate the corresponding **1(Br/I)**.

SCHEME 5. Variable Behavior of 6(Br) with *p*-Nitrobenzenesulfenyl Chloride or Benzeneselenyl Chloride Treatment



of **1(X/Y)**. In fact, neopentyl-like bromides **1(Br/H)** and **1(Br/Br)** did not undergo bromine substitution under zinc iodide treatment at the standard reaction conditions (CH_2Cl_2 solution at room temperature). That **1(Br/H)** or **1(Br/Br)** did not undergo bromine-by-chlorine substitution with benzeneselenyl chloride led us to reject a selenylating-reagent-induced free-radical mechanism. Moreover, addition of triphenylmethane, a free-radical scavenger,[19] did not have any influence on the reaction of **6(Br)** with benzeneselenyl chloride.

To explain this striking bromine substitution, we postulate an intramolecular bromine activation by its coordination (involving a six-member ring) with the electron-acceptor selenium center (Figure 2).[20]

This hypothesis was guaranteed by the easy chlorine substitution in **1(Cl/C_6H_5-Se)**, after treatment with zinc iodide, to give **1(I/C_6H_4-Se)**.[21]

Finally, as in other previously related cases,[11h] the presence of a strong Brönsted acid, together with the electrophilic reagent in the reaction media, could cause proton addition to be the major pathway, leading to 9-bromocamphor **1(Br/H)** as the major reaction product.

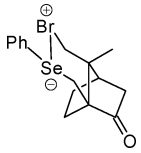


FIGURE 2. Postulated intramolecular activation for the nucleophilic bromine substitution of intermediate **1(Br/C_6H_5-Se)**.

This undesirable collateral reaction could also occur with easily hydrolyzable electrophilic reagents.

In summary, the reaction of readily accessible C(9)-substituted-camphor-derived 2-methylenenorbornan-1-ols **6(X)** with various electrophilic reagents takes place with an exquisitely stereocontrolled tandem carbon−carbon double-bond addition−Wagner-Meerwein rearrangement to yield C(9),C(10)-disubstituted camphors **1(X/Y)**. The reaction occurs under very mild conditions and with good yields.

This synthetic procedure constitutes a general and straightforward methodology for the access to valuable enantiopure C(9),C(10)-disubstituted camphors (including various susbstituted derivatives) and, therefore, for the access to new unexplored related camphor-derived chiral sources. Thus a highly efficient preparation of the well-known chiral key intermediate 9,10-dibromocamphor [**1(Br/Br)**] has been described and, for the first time, some novel C(9),C(10)-heteroatomically disubstituted camphors have been easily obtained, making unnecessary the use of tedious protection−deprotection group (carbonyl) strategies. These newly described C(9)-*halogen*/C(10)-*halogen*-, -*O*-, -*S*-, or -*Se*-substituted camphors will be valuable reagents for the preparation of novel C(9),C(10)-disubstituted camphor-derived chirality transfer agents.

In addition, an interesting intramolecular activation, for the nucleophilic substitution of neopentylic C(9)-bromo groups by the action of a C(10)-selenium, has been postulated for the first time. This activated substitution can also serve as a valuable synthetic tool for the preparation of various new C(9),C(10)-disubstituted camphors.

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Supporting Information Available: General experimental methods, specific synthetic procedures, as well as copies of ^1H and ^{13}C NMR spectra of the new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For example see: Ando, W.; Kako, M.; Akasaka, T.; Nagase, S.; Kawai, T.; Nagai, Y.; Sato, T. *Tetrahedron Lett.* **1989**, *30*, 6705−6708.

(20) Trost et al. have previously reported an unusual intramolecular selenium effect on the regiochemistry of a Baeyer−Villiger rearrangement: Trost, B. M.; Buchmayer, P.; Mao, M. *Tetrahedron Lett.* **1982**, *23*, 1443−1446.

(21) Zinc iodide treatment under standard conditions (CH_2Cl_2 solution at room temperature). The substitution reaction was pointed out by analyzing the reaction mixture by GC-MS.