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C(10)-Substituted Camphors and Fenchones by Electrophilic Treatment of 2-Methylenenorbornan-1-ols: Enantiospecificity, Scope, and Limitations

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Valuable chiral sources of C(10)-substituted camphors and C(10)-substituted fenchones can be straightforwardly obtained by treatment of an appropriate, easily obtainable, camphor- or fenchone-derived 2-methylenenorbornan-1-ol with an electrophilic reagent. The process takes place via a tandem regioselective carbon−carbon double-bond addition/stereocontrolled Wagner−Meerwein rearrangement. A complete study of the enantiospecificity, scope, and limitations of this process, as well as about the role played by the hydroxyl group attached at the C(1) bridgehead position of the starting 2-methylenenorbornan-1-ols, has been realized. The feasibility of the described methodology has been exemplified by the highly efficient enantiospecific preparation of several interesting C(10)-*halogen*-, C(10)-*O*-, C(10)-*S*-, C(10)-*Se*-, or C(10)-*C*-substituted camphors and fenchones.

Introduction

The naturally occurring ketones (+)-(1*R*)-camphor (**1**) and (−)-(1*R*)-fenchone (**2**) (Scheme 1) have been widely used as key intermediates for the synthesis of interesting optically enriched organic molecules, as well as for the construction of chiral auxiliaries, chiral catalysts, and chiral reagents for asymmetric synthesis.[1] This is due to (a) the abundance, and therefore low price, of these bicyclic terpenic ketones, (b) the facility to realize several functionalizations on the norbornane skeleton in a high stereocontrolled form,[1a,b] and (c) the fact that the rigid norbornane framework can easily undergo fragmentation, generally by the C(1)−C(2) or the C(2)−C(3) bond, to generate interesting chiral cyclopentanoids.[2] On the other hand, also the enantiomers (−)-(1*S*)-camphor (***ent*-1**) and (+)-(1*S*)-fenchone (***ent*-2**) are available, which enhances the utility of the camphor- and fenchone-based synthetic routes.

Among the great variety of camphor-derived chiral sources (generally C(2)-substituted camphors, see type II in Scheme 1),[3] the group of C(10)-substituted camphors (types IV and V) must be outlined. This is due to the fact that these kinds of camphor derivatives have been demonstrated to act as valuable chiral auxiliaries [e.g. Oppolzer's sultam (**3**)],[4] chiral catalysts [e.g. amino alcohol **4**],[5] and chiral reagents [e.g. Davis' oxaziridine (**5**)][6] for asymmetric synthesis, chiral resolving agents for the resolution of racemic mixtures (e.g. sulfonic acid **6**),[7] as well as key chiral intermediates for the total synthesis of natural products [e.g. 10-methylenecamphor (**7**) in

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(1) Some interesting general reviews are: (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (b) Money, T. *Nat. Prod. Rep.* **1985**, *2*, 253. (c) Ho, T.-L. In *Enantioselective Synthesis: Natural Products from Chiral Terpenes*; John Wiley and Sons: New York. 1992. (d) Money, T. In *Studies in Natural Products Chemistry*; Atta-ur-Rahmann, Ed.; Elsevier: Amsterdam, The Netherlands, 1989. (e) Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York. 1994. (f) Seyden-Penne J. In *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York. 1995.

(2) Some recent examples are the following: concerning the C1/C2 fragmentation: (a) Mermet-Mouttet, M. P.; Gabriel, K.; Heissler, D. *Tetrahedron Lett.* **1999**, *40*, 843. (b) Mehta, G.; Mohal, N. *Tetrahedron Lett.* **1999**, *40*, 5791 and 5795. (c) Mehta, G.; Venkateswaran, R. V. *Tetrahedron* **2000**, *56*, 1399. (d) Mehta, G.; Mohal, N. *Tetrahedron Lett.* **2001**, *42*, 4227. Concerning the C2/C3 fragmentation see: (e) Nagakawa, H.; Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 4523. (f) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945. Also see refs 1b and 8.

(3) For example see: (a) Palomo, C.; Oiarbide, M.; Sharma, A. K.; González-Rego, M. C.; Linden, A.; García, J. M.; González, A. *J. Org. Chem.* **2000**, *65*, 9007. (b) Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063. (c) Xu, Q.; Wang, G.; Pan, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 381. (d) Dimitrov, V.; Dobrikov, G.; Genov, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1323. (e) Malaisè, G.; Barloy, L.; Osaborn, J. A. *Tetrahedron Lett.* **2001**, *42*, 7417. (f) Hung, S.-C.; Wen, Y.-F.; Chang, J.-W.; Liao, C.-C.; Vang, B.-J. *J. Org. Chem.* **2002**, *67*, 1308.

(4) Among the great number of examples concerning to the use of Oppolzer's sultame, some modern ones are: (a) Sasaki, H.; Carreira, E. M. *Synthesis* **2000**, 135. (b) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (c) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953. (d) Szymansky, S.; Chapuis, C.; Jurczak, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1939. (e) Jullian, V.; Monjardet Bas, V.; Fosse, C.; Lavielle, S.; Chassaing, G. *Eur. J. Org. Chem.* **2002**, 1677. (f) Schmidt, B.; Wildermann, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1050. (g) Karlsonn, S.; Högberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1076.

(5) (a) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4127 and 2971. (b) Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2000**, *41*, 4587.

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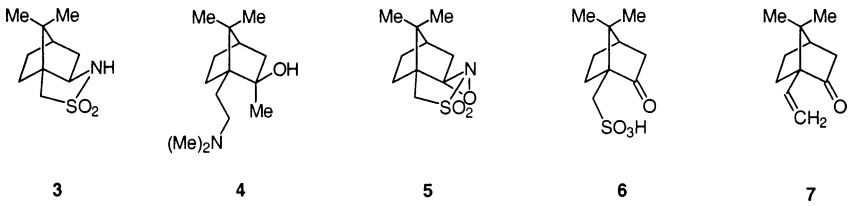
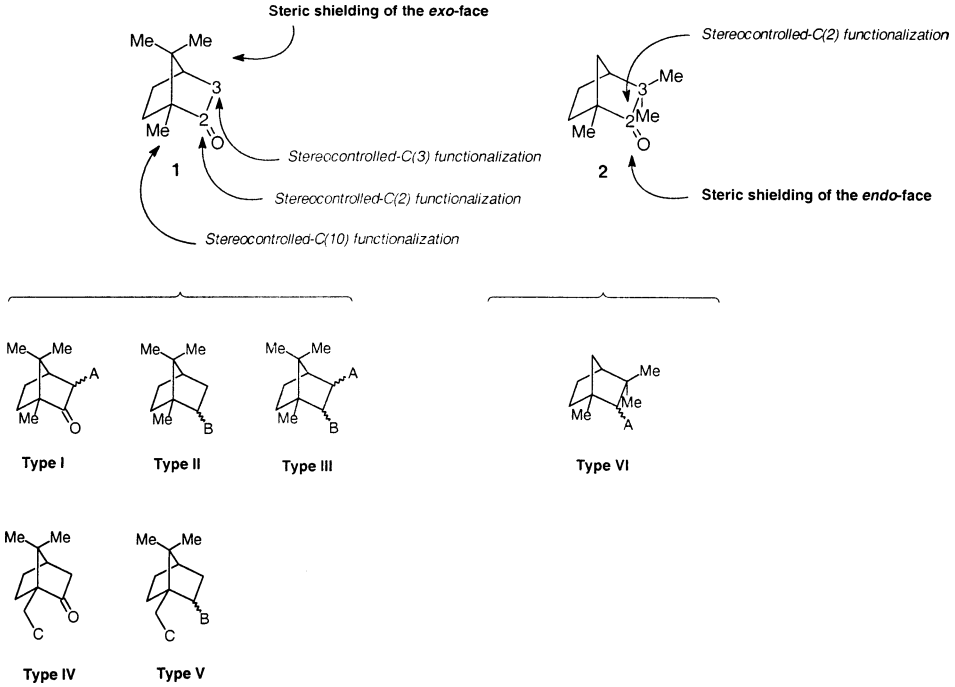


FIGURE 1. Some relevant C(10)-substituted camphor-based chiral sources.

SCHEME 1. Main Types of Nonracemic Camphor and Fenchone Derivatives by Stereocontrolled Functionalization of (+)-Camphor (1) and (−)-Fenchone (2)



Paquette's approach to the anticancer natural product taxol][8] (Figure 1). Most of the C(10)-substituted camphors are C(10)-*S*-substituted, mainly C(10)-*S*(VI)-substituted (e.g. **3**, **5**, and **6** in Figure 1). This is due to the fact that almost all of the synthetic routes described for the preparation of these kinds of camphor derivatives use commercial enantiopure 10-camphorsulfonic acid (**6**) (the first C(10)-substituted camphor derivative obtained),[9] or enantiopure 10-camphorsulfonyl chloride, as starting material. Nevertheless, several modern enantiopure camphor ligands with a C(10)-substitution different from the common C(10)-*S*, such as C(10)-*O*-, C(10)-*N*-, C(10)-*halogen*-, C(10)-*P*-, C(10)-*Se*-, C(10)-*Te*-, or C(10)-*C*-, also have been described as interesting chiral sources (e.g. **4** and **7** in Figure 1).[10] In these last cases, the necessity of using **6**, or other derivatives obtained from it, as the starting material makes most of those synthetic routes result in low overall yields.[10]

On the other hand, despite the complementarities existing between camphor- and fenchone-derived chirality transfers,[11] C(10)-substituted fenchones have not been obtained, nor probed. This is due to the fact that enantiopure 10-fenchonesulfonic acid (the fenchone analogue of **6** and, therefore, the potential key starting

(6) Some modern examples are: (a) Tagami, K.; Nakazawa, N.; Sano, S.; Nagao, Y. *Heterocycles* **2000**, *53*, 771. (b) Wang, C.-C.; Li, J. J.; Huang, H.-C.; Lee, L. F.; Reitz, D. B. *J. Org. Chem.* **2000**, *65*, 2711. (c) Pabmanabhan, S.; Lavin, R. C.; Durant, G. J. *Tetrahedron: Asymmetry* **2000**, *11*, 3455.

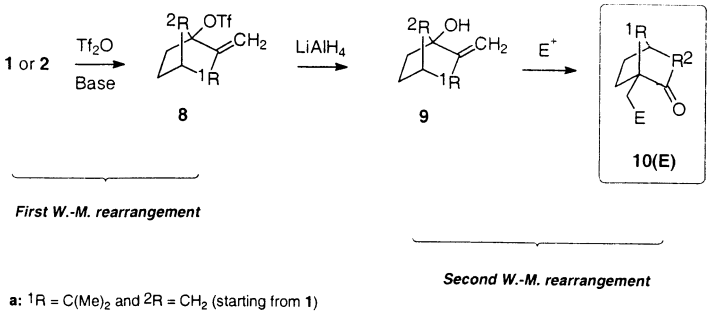
(7) As examples, see: (a) Cermak, D. M.; Du, Y.; Wiemer, D. *J. Org. Chem.* **1999**, *64*, 388. (b) Yoshioka, R.; Hiramatsu, H.; Okamura, K.; Tsujioka, I.; Yamada, S.-I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2121. (c) Kaptein, B.; Elsenberg, H.; Gringergen, R. F. P.; Broxterman, Q. B.; Hulshof, L. A.; Pouwer, K. L.; Vries, T. R. *Tetrahedron: Asymmetry* **2000**, *11*, 1343. (d) Bàlint, J.; Hell, Z.; Markovits, I.; Pàrkànyi, L.; Fogassy, E. *Tetrahedron: Asymmetry* **2000**, *11*, 1323. (e) Andersen, N. G.; Ramsden, P. D.; Che, D.; Parvez, M.; Keay, B. A. *J. Org. Chem.* **2001**, *66*, 7478.

(8) (a) Paquette, L. A.; Zhao, M.; Montgomery, F.; Zeng, Q.; Wang, T. Z.; Elmore, S.; Combink, K.; Wang, H.-L.; Bailey, S.; Zhuang, S. *Pure Appl. Chem.* **1998**, *70*, 1449. (b) Paquette, L.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203. (c) Paquette, L.; Zeng, Q.; Wang, H.-L.; Shih, T.-L. *Eur. J. Org. Chem.* **2000**, 2187.

(9) Reychler, A. *Bull. Soc. Chim. Paris* **1898**, *19*, 120.

(10) For example, see the following: Referred to C(10)-*O*-substituted camphors: (a) Chu, Y.-Y.; Yu, C.-S.; Chen, C.-J.; Yang, K.-S.; Lian, J.-C.; Lin, C.-H.; Chen, K. *J. Org. Chem.* **1999**, *64*, 6993. (b) Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2001**, *12*, 3067. Referred to C(10)-*N*-substituted camphors: (c) Seo, R.; Ishizuka, T.; Abdel-Aziz, A. A.-M.; Kunieda, T. *Tetrahedron Lett.* **2001**, *42*, 6353. (d) Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837. (e) Yang, K.-S.; Chen, K. *J. Org. Chem.* **2001**, *66*, 1676. Referred to C10-*halogen*-substituted camphors: (f) Fergurson, C. G.; Money, T.; Portillo, J.; Whitelaw, P. D. M.; Wong, M. K. C. *Tetrahedron* **1996**, *52*, 14461. Referred to C(10)-*P*-substituted camphors: (g) Komarov, I. V.; Gorichko, M. V.; Kornilov, M. *Tetrahedron: Asymmetry* **1997**, *8*, 435. (h) Sell, T.; Laschat, S.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2000**, 4119. (i) Monsess, A.; Laschat, S. *Synlett* **2002**, 1011. Referred to C(10)-*Se*-substituted camphors: (j) Takahashi, T.; Nakao, N.; Koizumi, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3293. (k) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1. Referred to C(10)-*Te*-substituted camphors: (l) Zhang, J.; Saito, S.; Koizumi, T. *J. Org. Chem.* **1998**, *63*, 5423. Referred to C(10)-*C*-substituted camphors, see refs 5 and 8.

SCHEME 2. Straightforward Preparation of C(10)-Substituted Camphors and Fenchones from Camphor (1) and Fenchone (2)



a: $^1R = C(Me)_2$ and $^2R = CH_2$ (starting from **1**)
b: $^1R = CH_2$ and $^2R = C(Me)_2$ (starting from **2**)

material for other C(10)-substituted fenchones) is not commercially available.[12]

From all the above, it is easy to understand that the establishment of a straightforward synthetic route to both nonracemic C(10)-substituted camphors and fenchones is of a great interest. In this sense, and related to our interest in the synthetic applications of the Wagner−Meerwein rearrangement in the preparation of bridgehead norbornane derivatives, starting from readily available (+)-camphor **1** and (−)-fenchone **2**,[13] we have recently reported in some communications a new and versatile synthetic route to these kinds of derivatives (Scheme 2).[14] The established route includes two key stereocontrolled Wagner−Meerwein rearrangements: (1) a first base-controlled triflic-anhydride-promoted Wagner−Meerwein rearrangement of the starting optically active 1-methylnorbornan-2-one (**1** or **2**) to produce the corresponding bridgehead 2-methylenenorborn-1-yl triflate **8** and (2) a second electrophile-promoted Wagner−Meerwein rearrangement of 2-methylenenorbornan-1-ols **9** to yield the corresponding C(10)-substituted camphor or fenchone **10(E)**.

In this paper we provide insight into the enantiospecificity, scope, and limitations of the second Wagner−Meerwein rearrangement of the above-described route [i.e. the rearrangement of **9** upon treatment with the electrpophilic reagent (E^+)], for the preparation of enaniomerically pure, or enantiomerically enriched, C(10)-substituted camphors and fenchones [**10(E)**].

Results and Discussion

(1) Enantiospecificity. In an earlier publication in 1901,[15] Forster described that the treatment of an optically active camphor-derived alcohol of unknown structure [nowadays we know such alcohol is 3,3-dimethyl-2-methylenenorbornan-1-ol (**9a**)] with an excess of ice-cooled sulfuric acid gave enantiopure camphor (**1**),[16] which constitutes the first example of the reaction considered herein (see Scheme 2, $E^+ = H^+$, **10a(H)** = **1**). The enantiospecificity of Forster's result contrasts with the well-known fact that Wagner−Meerwein rearrangement of 3,3-dimethylnorborn-2-yl carbocations use to be accompanied by a competitive Nametkin rearrangement, consecutive 6,2-hydride shift between enantiomeric carbocations, and subsequent carbocation rearrangements, which are conducive to the formation of racemic mixtures, or, at least, products with a low optical purity (scalemic mixtures).[17] Thus, the addition of a proton to the carbon−carbon double bond of 3,3-dimethyl-2-methylenenorbornan-1-ol (**9a**) could take place with a Wagner−Meerwein rearrangement to give enantiopure (1*R*)-camphor (**1**), or with both Wagner−Meerwein and competitive Nametkin rearrangements to give **1** together with a certain amount of its enantiomer (***ent*-1**) (Scheme 3).

In this sense, we have also repeated such a rearrangement, treating now enantiopure **9a** with 10% HCl. In

(11) For the influence of the topological differences of camphor- and fenchone-derived chiral sources on the chirality transfer, see: (a) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron Asymmetry* **1997**, *8*, 1869. (b) Suzuki, Y.; Ogata, Y.; Hiroi, K. *Tetrahedron: Asymmetry* **1999**, *10*, 1219. (c) Page, P. C. B.; Murrell, V. L.; Limousin, C.; Laffan, D. D. P.; Bethell, D.; Slawin, A. M. Z.; Smith, T. A. D. *J. Org. Chem.* **2000**, *65*, 4204. Also see refs 5 and 13g.

(12) For the preparation of 10-fenchonesulfonic acid, see: Verfürth, V.; Ugi, I. *Chem. Ber.* **1991**, *124*, 1627.

(13) (a) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Díaz Oliva, C.; Subramanian, L. R.; Maichle, C. *Tetrahedron: Asymmetry* **1994**, *5*, 949. (b) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1994**, *5*, 1373. (c) García Martínez, A.; Subramanian, L. R.; Hanack, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 7, p 5146. (d) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1257. (e) García Martínez, A.; Teso Vilar, E.; Moreno Jímenez, F.; Martínez Bilbao, C. *Tetrahedron: Asymmetry* **1997**, *8*, 3031. (f) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Herrera Fernández, A.; de la Moya Cerero, S.; Moreno Jiménez, F. *Tetrahedron* **1998**, *54*, 6539. (g) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1737. (h) García Martínez, A.; Teso Vilar, E.; Moreno Jímenez, F.; García Amo, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1709. (i) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Martínez Ruiz, P. *Eur. J. Org. Chem.* **2001**, 2805. (j) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Martínez Ruiz, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2153. (k) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Chicharro Villas, P. *Tetrahedron: Asymmetry* **2002**, *13*, 1.

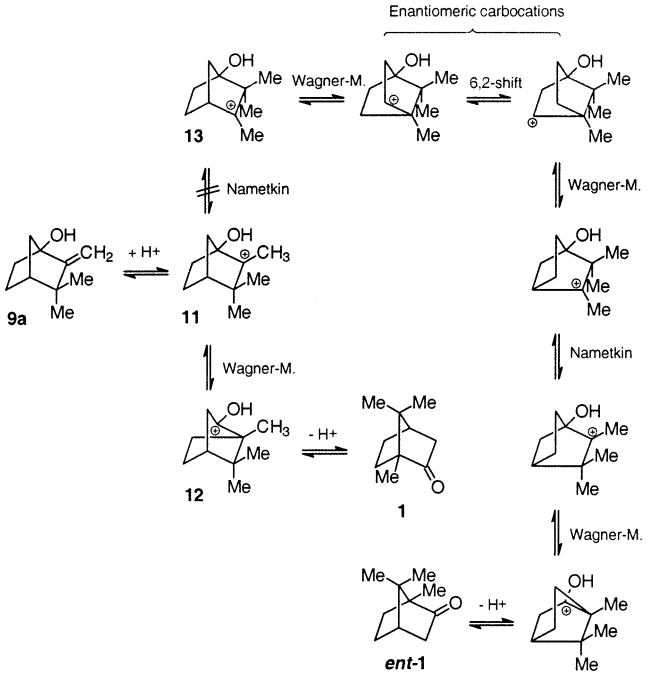
(14) (a) Lora Maroto, B.; de la Moya Cerero, S.; García Martínez, A.; García Fraile, A.; Teso Vilar, E. *Tetrahedron: Asymmetry* **2000**, *11*, 3059. (b) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2000**, *11*, 4437. (c) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron Lett.* **2001**, *42*, 5017. (d) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron Lett.* **2001**, *42*, 6539. (e) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2001**, *12*, 3325. (f) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron Lett.* **2002**, *43*, 1183.

(15) Forster, M. O. *J. Chem. Soc.* **1901**, *79*, 644.

(16) The obtained camphor was identified as the corresponding enantiopure oxime with $[\alpha]_D$ −40.2 in absolute ethanol.

(17) Some examples are: (a) Eck, R.; Mills, R. W.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 521. (b) Money, T.; Palme, M. H. *Tetrahedron: Asymmetry* **1993**, *4*, 2363. Also see ref 13f.

SCHEME 3. Possible Reaction Pathways for the Proton Addition to 3,3-Dimethylated 2-Methylenenorbornan-1-ol 9a



agreement with Forster's result, enantiopure (1*R*)-camphor (**1**) was obtained in approximately quantitative yield (Scheme 3). In both cases, the reached enantiospecificity can be explained by the presence of the electron-donating hydroxyl group (+K effect) attached to the C(1) position in the initial carbocation **11** (Scheme 3). Thus, such a hydroxyl group must stabilize the new carbocation formed after the Wagner−Meerwein rearrangement of **11** (i.e. the 2-norbornyl cation **12**), which makes the Wagner−Meerwein process much more rapid than the competitive Nametkin rearrangement to less stable carbocation **13** (see Scheme 3).[18]

(2) Scope. Forster also essayed the addition of bromine to his optically active camphor-derived alcohol (i.e. enantiopure **9a**),[15] obtaining an optically active bromoketone that was identified as 6-bromocamphor,[19] although it was really enantiopure 10-bromocamphor [**10a(Br)**] (see Scheme 2).[20,21a] Unfortunately, the addition of bromine to **9a** produces camphor (**1**) as a secondary product, due to the formation of hydrogen bromide during the course of the reaction. This problem can be avoided by using pyridine as the solvent, which acts as a scavenger of the formed acid.[18a] Nevertheless, this methodology has not been employed as the common procedure to obtain enantiopure **10a(Br)**, a valuable key intermediate to other C(10)-substituted camphors,[21] probably due to the difficulties and low yield in obtaining the enantiopure starting material **9a**.[15,22] On the other hand, this procedure presents the unsuitability of using very reactive and toxic bromine as the electrophilic reagent.

TABLE 1. Electrophilic Treatment of 2-Methylenenorbornan-1-ols 9a and 9b: Enantiospecific Preparation of C(10)-Substituted Camphors [10a(E)] and C(10)-Substituted Fenchones [10b(E)]

starting alcohol	reagent	reaction product	yield (%)
9a	NCS	**10a(Cl)**	73
9b	NCS	**10b(Cl)**	87
9a	NBS	**10a(Br)**	96
9b	NBS	**10b(Br)**	96
9a	NIS[a]	**10a(I)**	67
9b	NIS[a]	**10b(I)**	86
9a	*m*-CPBA	**10a(OH)**	78
9b	*m*-CPBA	**10b(OH)**	82
9a	*p*-NO_2-C_6H_4-SCl	**10a(*p*-NO_2-C_6H_4-S)**	70
9b	*p*-NO_2-C_6H_4-SCl	**10b(*p*-NO_2-C_6H_4-S)**	95
9a	C_6H_5-SeCl	**10a(C_6H_5-Se)**	82
9b	C_6H_5-SeCl	**10b(C_6H_5-Se)**	88
9a	$[CH_2{=}NMe_2]^+,I^-$	**10a(CH_2NMe_2)**	98
9b	$[CH_2{=}NMe_2]^+,I^-$	**10b(CH_2NMe_2)**	97

[a] NIS = *N*-iodosuccinimide.

We have found that such problems can be avoided using (a) our straightforward methodology for the preparation of enantiopure **9a** (see Scheme 2) and (b) *N*-bromosuccinimide (NBS) as the electrophilic brominating reagent instead of bromine. Thus, the reaction of **9a** with NBS takes place enantiospecifically and in mild reaction conditions (methylene dichloride/room temperature) to give **10a(Br)** as the only reaction product in high yield (Scheme 4).[14a] The use of a base, such as pyridine, is now not necessary, since during the course of the reaction succinimide, a weak acid, is formed instead of hydrogen bromide. Analogously, 10-chlorocamphor [**10a(Cl)**] and 10-iodocamphor [**10a(I)**] can be easily obtained from **9a** by using *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS), respectively, instead of NBS (see Table 1).

This exposed synthetic methodology has been extended to other electrophilic reagents, such as *m*-chloroperoxybenzoic acid (*m*-CPBA), *p*-nitrobenzenesulfenyl chloride, benzeneselenyl chloride, and *N*,*N*-dimethylmethaniminium iodide (Eschenmoser's salt), which has allowed the straightforward preparation of several interesting enantiopure C(10)-substituted camphors [**10a(E)**], such as C(10)-*O*-, C(10)-*S*-, C(10)-*Se*-, and C(10)-*C*-substituted camphors (see Table 1). On the other hand, fenchone-derived 2-methylenenorbornan-1-ol **9b** can be used instead of **9a**, which allows the preparation of the corresponding optically active C(10)-substituted fenchones [**10b(E)**] (see Table 1).

It is interesting to note that, when 3,3-dimethyl-2-methylenenorbornan-1-ol (**9a**) is reacted with other electrophiles (E^+) different from a proton, formation of scalemic mixtures of the corresponding C(10)-substituted camphor is not possible (cf. Schemes 3 and 4). This is due to the fact that the possible competitive Nametkin rearrangement of the initially formed 2,3,3-trimethylnorborn-2-yl carbocations [**14(E)**] would give a subse-

(18) This bridgehead-substituent effect has been previously demonstrated in: (a) Paukstelis, J. V.; Macharia, B. W. *Chem. Commun.* **1970**, 131. Also see: (b) Thomas, A. A.; Monk, K. A.; Abraham, S.; Lee, S.; Garner, C. M. *Tetrahedron Lett.* **2001**, *42*, 2261. (c) Gosselin, P.; Lelièvre, M.; Poissonnier, B. *Tetrahedron: Asymmetry* **2001**, *12*, 2091.

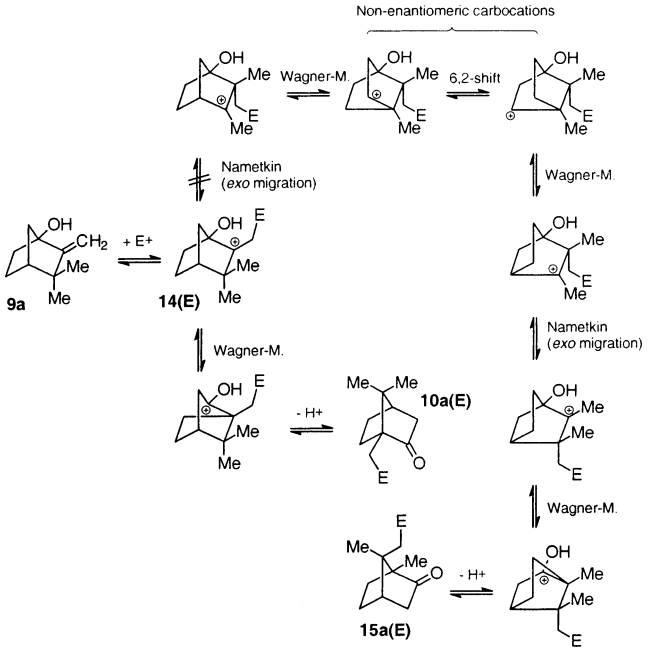
(19) Forster, M. O. *J. Chem. Soc.* **1902**, *81*, 264.

(20) By the measurement of the specific optical rotation.

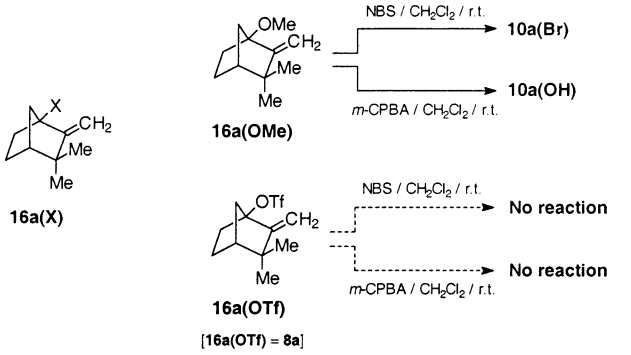
(21) The bromine atom of **10a(Br)** can be easily replaced by other functional groups via a nucleophilic-substitution reaction. As an example see: Dallacker, F.; Alroggen, I.; Krings, H.; Laurs, B.; Lipp. M. *Liebigs Ann. Chem.* **1961**, *647*, 23. Also see refs 10g,h,j, l.

(22) (a) Libman, J.; Sprecher, M.; Mazur, Y. *Tetrahedron* **1969**, *25*, 1679. Nonoptically pure **9a** can be obtained in better yield through another synthetic route (see ref 18a and references therein).

SCHEME 4. Possible Reaction Pathways for the Electrophile-Different-to-Proton Addition to 3,3-Dimethylated Norbornan-1-ol 9a



SCHEME 5. Behavior of 2-Methylenenorbornanes 16a(OMe) and 16a(OTf) under NBS and *m*-CPBA Treatment



quent 6,2-hydride shift between different (nonenantiomeric) carbocations (Scheme 4). But, by the same reasoning, C(8)-substituted camphors [**15a(E)**] could be now obtained (Scheme 4).[23]

Nevertheless, in all the studied reactions (see Table 1) C(8)-substituted camphors [**15a(E)**] have not been detected. Once again, the control of the reaction pathway is due to the electronic effect exerted by the hydroxyl group attached at the C(1) position of the initially formed 2-norbornyl carbocation **14(E)**, which favors the Wagner−Meerwein rearrangement over a possible competitive Nametkin rearrangement (see Scheme 4).

On the other hand, it has been previously reported that the reaction of some C(1)-substituted 3,3-dimethyl-2-methylenenorbornanes [**16a(X)**] (Scheme 5), such as 3,3-dimethyl-2-methylenenorbornane [**16a(H)**] or 1-chloro-3,3-dimethyl-2-methylenenorbornane [**16a(Cl)**], with different electrophiles, such as I^+, Cl^+ or Br^+, takes place with formation of mixtures of reaction products,[18a,24] whereas the reaction of 1-acetoxy-2-methylenenorbornane [**16a(OAc)**] with bromine generates 10-bromocamphor [**10a(Br)**].[18a] To gain an insight into the influence that the presence of a electron-donating group attached at the C(1) position of 3,3-dimethyl-2-methylenenorbornanes has on the behavior of these derivatives under electrophilic treatment, we have comparatively studied the addition of NBS and *m*-CPBA to the 3,3-dimethyl-2-methylenenorbornanes **16a(OMe)** and **16a(OTf)**, C(1)-methoxy and C(1)-triflyloxy subtituted, respectively (Scheme 5).

When 2-methylenenorbornane **16a(OMe)**, with an electron-donating methoxyl group attached to the C(1) position, is treated with NBS or *m*-CPBA, in the same reaction conditions in which bridgehead norbornane-based alcohol of identical structure **9a** was reacted, corresponding enantiopure 10-bromocamphor [**10a(Br)**] and 10-hydroxycamphor [**10a(OH)**] were obtained, respectively, as the only reaction products (Scheme 5). On the other hand, electron-withdrawing triflate **16a(OTf)** does not react under the same electrophilic treatments and reaction conditions.[25] Therefore, the presence of the activating electron-donating group at the C(1) position is necessary, not only for promoting the Wagner−Meerwein rearrangement,[18a] avoiding a possible competitive nondesirable Nametkin rearrangement, but also for activating the initial electrophilic addition to the carbon−carbon double bond.

In most cases, the presence of trace amounts of a strong Brönsted acid, together with the electrophilic reagent in the reaction media makes the major process the proton addition, giving the formation of camphor (**1**) or fenchone (**2**), respectively, as the only reaction product. This undesirable collateral reaction usually occurs with easily hydrolyzable electrophilic reagents, such as some strong Lewis' acids (e.g. SO_3, $AlCl_3$, BF_3, Meerwein's salt, etc.).

Summary

We have shown that the electrophilic treatment of the 2-methylenenorbornan-1-ols **9**, which are easily and enantiospecifically obtained from commercial camphor (**1**) or fenchone (**2**), takes place with a stereocontrolled tandem carbon−carbon double-bond addition/Wagner−Meerwein rearrangement, to give the corresponding C(10)-substituted camphors **10a(E)** and C(10)-substituted fenchones **10b(E)**. The reaction occurs under very mild conditions and with good-to-excellent yields. The electron-donating hydroxyl group attached to the C(1) norbornane position of the starting 2-methylenenorbornanes **9** is necessary to promote both the electrophilic

(23) C(8)-substituted camphor derivatives are spectroscopically quite different from the corresponding C(10)-substituted camphors. As an example, see the described spectroscopic data for 8-bromocamphor [**15a(Br)**] in ref 17a.

(24) In relation to I^+ see: (a) Bochwic, B.; Kuswik, G.; Olejniczak, B. *Tetrahedron* **1975**, *31*, 1607. In relation to Cl^+ see: (b) Masson, S.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1969**, 4368. (c) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265. (d) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273. (e) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 1206. See also: (f) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(25) 2-Methylenenorborn-1-yl triflate **16a(OTf)** is able to react with *m*-CPBA under more energetic conditions (refluxing methylene dichloride) to yield the corresponding nonrearranged spiranic oxirane as a mixture of epimers: García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B.; Díaz Morillo, C. *Tetrahedron Lett.* **2001**, *42*, 8293.

addition to the carbon−carbon double bond and the subsequent Wagner−Meerwein rearrangement, as well as to avoid the formation of mixtures of isomers.

The described process has allowed the highly efficient preparation of interesting C(10)-heteroatom-substituted camphors, such as 10-bromocamphor [**10a(Br)**] or 10-hydroxycamphor [**10a(OH)**],[26] which are valuable intermediates to other enantiopure C(10)-substituted camphors.[14a,b] On the other hand, the reaction of **9a** with *p*-nitrobenzenesulfenyl chloride and benzeneselenyl chloride constitutes a new model procedure for the enantiospecific preparation of valuable C(10)-*S*- and C(10)-*Se*-substituted camphor-derived chiral sources.[14c] We also have been able to form a new carbon−carbon bond at the C(10) position of the camphor skeleton by using an iminium salt (Eschenmoser's salt) as the electrophilic reagent, which allows the preparation of interesting C(10)-*C*-substituted camphor-derived chiral sources.[14f] In this sense, derivative **10a(CH_2NMe_2)** has been recently used by us as the chiral key precursor of the taxoid-intermediate 10-methylenecamphor (**7**).[27]

Finally, the extension of the above-described reactivity to optically active 2-methylenenorbornan-1-ol **9b**, instead of **9a**, has allowed the easy enantiospecific access to the C(10)-substituted fenchone-derived chiral sources.[14d,e]

Experimental Section

General Information. All starting materials and reagents were obtained from well-known commercial suppliers and were used without further purification. Ether and THF were dried by distillation over sodium/benzophenone, under argon atmosphere, immediately prior to use. CH_2Cl_2 and $CHCl_3$ were dried by distillation over P_2O_5. Flash chromatography was performed over silica gel (230−400 mesh) or neutral aluminum oxide (150 mesh). ^1H and ^{13}C NMR were recorded on a 200-MHz spectrometer for ^1H and on a 50-MHz spectrometer for ^1H or ^{13}C. Chemical shifts (δ) for ^1H and ^{13}C NMR were recorded in ppm downfield relative to the internal standard tetramethylsilane (TMS), and coupling constants (J) are in Hz. IR spectra were recorded on a FT spectrometer. Mass spectra were recorded on a 60-eV mass spectrometer. HRMS were recorded by using the FAB technique. For gas−liquid chromatography (GLC), a chromatograph equipped with a capillary silicon-gum column (TRB-1) was used.

(1*R*)-3,3-Dimethyl-2-methylenenorbornan-1-ol (9a). Alcohol **9a**[22] was prepared by LAH reduction of triflate **8a**,[28] according to a general procedure previously described by us.[29]

(1*S*)-7,7-Dimethyl-2-methylenenorbornan-1-ol (9b). Following the above-described procedure for the preparation of **9a**,[29] 5.00 g (17.6 mmol) of triflate **8b**[28,30] was reacted with lithium aluminum hydride for 24 h. After standard hydrolysis, extraction, washing, drying, filtration, and solvent evaporation, the obtained residue was purified by column chromatography (silica gel, hexane/ether 50:50) to yield pure **9b**[30] (2.57 g, 96% yield) as a white solid: Mp 55−57 °C. $[\alpha]^{20}_D$ −2[30] (0.51, CH_2Cl_2). FTIR (CCl_4) ν 3412 (br), 3074, 2955, 1664, 1148 cm^{-1}. MS m/z 152 ($M^{+\bullet}$, 9). HRMS 152.1204 [calcd for $C_{10}H_{16}O$ 152.1201]. ^1H NMR ($CDCl_3$, 200 MHz) δ 4.98 (dd, J = 2.4, J = 2.4, 1H), 4.76 (dd, J = 2.1, J = 2.1, 1H), 2.44 (dm, J = 16.5, 1H), 2.01 (ddd, J = 16.4, J = 2.1, J = 2.1, 1H), 1.93−1.81 (m, 2H), 1.77 (s, 1H), 1.68 (dd, J = 4.3, J = 4.3, 1H), 1.54−1.43 (m, 1H), 1.34−1.23 (m, 1H), 1.00 (s, 3H), 0.84 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.8, 101.4, 85.9, 46.0, 40.9, 35.5, 32.4, 27.2, 18.5, 18.0 ppm.

Treatment of 2-Methylenenorbornan-1-ol 9a with HCl. A suspension of **9a** (152 mg, 1.0 mmol) in 10 mL of 10% HCl was stirred at room temperature for 6 h (the reaction progress was monitored by GLC). Finally, the reaction mixture was diluted with 15 mL of water and extracted with CH_2Cl_2. The organic layer was washed with saturated sodium hydrogencarbonate solution and with brine, and dried over anhydrous magnesium sulfate. After filtration and solvent evaporation, pure **1** (150 mg, approximately quantitative yield) was obtained. Optical purity (>98%) was determined by measurement of the specific optical rotation in comparison with that obtained from a pure sample of commercial **1**.

(1*S*)-10-Chlorocamphor [10a(Cl)]. A solution of **9a** (152 mg, 1.0 mmol) and NCS (147 mg, 1.1 mmol) in 10 mL of dry CH_2Cl_2 was stirred at room temperature for 48 h (the reaction time was monitored by GLC). Finally, the reaction mixture was poured into 15 mL of saturated sodium hydrogencarbonate solution and extracted with CH_2Cl_2. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. After filtration and solvent evaporation, the residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 50:50) to yield pure **10a(Cl)** (136 mg, 73% yield) as a white solid. Mp 110−111 °C. $[\alpha]^{20}_D$ +38 (0.22, CH_2Cl_2). FTIR (CCl_4) ν 2962, 1742, 1390 cm^{-1}. MS m/z 186 [$M^{+\bullet}$(^{35}Cl), 3], 188 [$M^{+\bullet}$(^{37}Cl), 1]. HRMS m/z 186.0806 [calcd for $C_{10}H_{15}OCl$ (^{35}Cl) 186.0811]. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.79 (AB, J = 12.1, 1H), 3.60 (AB, J = 12.1, 1H), 2.41 (ddd, J = 18.3, J = 4.4, J = 2.2, 1H), 2.22−1.95 (m, 3H), 1.74 (d, J = 18.3, 1H), 1.55−1.33 (m, 2H), 1.12 (s, 3H), 0.97 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 215.9, 61.6, 47.8, 43.9, 43.1, 41.4, 26.7, 26.2, 20.5, 20.4 ppm.

(1*S*)-10-Chlorofenchone [10b(Cl)]. Following the above-described procedure for the preparation of **10a(Cl)**, 152 mg (1.0 mmol) of **9b** was reacted with NCS with a reaction time of 48 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(Cl)**], the obtained residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 50:50) to yield pure **10b(Cl)**[30] (162 mg, 87% yield) as a colorless liquid: $[\alpha]^{20}_D$ −16[30] (0.23, CH_2Cl_2). FTIR (CCl_4) ν 2970, 1744, 1385 cm^{-1}. MS m/z 186 [$M^{+\bullet}$(^{35}Cl), 5], 188 [$M^{+\bullet}$(^{37}Cl), 2]. HRMS m/z 186.0817 [calcd for $C_{10}H_{15}OCl$ (^{35}Cl) 186.0811]. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.83 (AB, J = 11.6, 1H), 3.63 (AB, J = 11.6, 1H), 2.20 (br s, 1H), 2.02 (ddd, J = 10.7, J = 1.9, J = 1.9, 1H), 1.95−1.69 (m,

(26) Both enantiopure 10-bromocamphor [**10a(Br)**] and 10-hydroxycamphor [**10a(OH)**] have been previously prepared from 10-camphorsulfonic acid in a very low overall yield (20% and 12%, respectively) according to the procedure described by Dallacker in ref 21. Alcohol **10a(OH)** can be also prepared in 72% yield from β-pinene oxide (Villemin, D.; Hammandi, M. *Synth. Commun.* **1995**, *25*, 3141).

(27) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2002**, *13*, 17.

(28) For the enantiospecific synthesis of triflates **8a** and **8b**, 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 the nonnucleophilic base instead of *N*,*N*-diisobutyl-2,4-dimethyl-3-pentanamine, which is no longer commercially available.

(29) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Ruano Franco, C.; Soto Salvador, J.; Subramanian, L. R.; Hanack, M. *Synthesis* **1987**, 321.

(30) Since the starting commercial (−)-fenchone (**2**) has an ee of 82%, all products enantiospecifically obtained from it [i.e. **8b**, **9b**, and **10b(E)**] must possess the same opticaly purity. This fact has been tested for the case of **10b(OH),** by comparison of the obtained specific optical rotation with the measured one for enantiopure 10-hydroxyfenchone (see ref 32b).

(31) Enantiopure **10a(I)** has been previously prepared from 10-camphorsulfonyl chloride (Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* **1983**, *7*, 3553).

(32) 10-Hydroxyfenchone has been previously prepared from fenchone following a six-step route with low overall yield: (a) Paquette, L. A.; Teleha, C. A.; Taylos, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 265 and references therein. Enantiopure 10-hydroxyfenchone has been described as the major metabolite in the biotransformation of (+)-camphor in rabbits: (b) Miyazawa, M.; Kameoka, H. *Chem. Express* **1988**, *3*, 503.

3H), 1.69 (dd, $J = 10.5$, $J = 1.9$, 1H), 1.37−1.23 (m, 1H), 1.05 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 219.8, 59.6, 48.2, 44.9, 43.6, 38.1, 27.9, 24.8, 23.0, 21.5 ppm.

(1*S*)-10-Bromocamphor [10a(Br)]. Following the above-described procedure for the preparation of **10a(Cl)**, 152 mg (1.0 mmol) of **9a** was reacted with NBS instead of NCS with a reaction time of 24 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(Cl)**], the obtained residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 50:50) to yield pure **10a(Br)**[15,21a] (222 mg, 96% yield).

(1*S*)-10-Bromofenchone [10b(Br)]. Following the above-described procedure for the preparation of **10a(Cl)**, 152 mg (1.0 mmol) of **9b** was reacted with NBS instead of NCS with a reaction time of 24 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(Cl)**], the obtained residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 50:50) to yield pure **10b(Br)**[30] (222 mg, 96% yield) as a colorless liquid: $[\alpha]^{20}_D$ −3[30] (0.31, CH_2Cl_2). FTIR (film) ν 2926, 1740, 1385 cm^{-1}. MS *m*/*z* 230 [M$^{+\bullet}$(^{79}Br), 3], 232 [M$^{+\bullet}$(^{81}Br), 3]. HRMS *m*/*z* 230.0303 [calcd for $C_{10}H_{15}OBr$ (^{79}Br) 230.0306]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.71 (AB, $J = 10.7$, 1H), 3.51 (AB, $J = 10.7$, 1H), 2.19 (br s, 1H), 2.08−1.98 (dm, $J = 10.5$, 1H), 1.94−1.70 (m, 3H), 1.70 (dd, $J = 10.5$, $J = 1.9$, 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.

(1*S*)-10-Iodocamphor [10a(I)]. Following the above-described procedure for the preparation of **10a(Cl)**, 152 mg (1.0 mmol) of **9a** was reacted with NIS instead of NCS with a reaction time of 2 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(Cl)**], the obtained residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 50:50) to yield pure **10a(I)**[31] (186 mg, 67% yield).

(1*S*)-10-Iodofenchone [10b(I)]. Following the above-described procedure for the preparation of **10a(Cl)**, 152 mg (1.0 mmol) of **9b** was reacted with NIS instead of NCS with a reaction time of 2 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(Cl)**], the obtained residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 50:50) to yield pure **10b(I)**[30] (239 mg, 86% yield) as a colorless liquid: $[\alpha]^{20}_D$ +10[30] (0.22, CH_2Cl_2). FTIR (film) ν 2968, 1742, 1383 cm^{-1}. MS *m*/*z* 151 (M$^{+\bullet}$ − I, 18). HRMS *m*/*z* 278.0169 (calcd for $C_{10}H_{15}OI$ 278.0168). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.49 (AB, $J = 10.5$, 1H), 3.31, (AB, $J = 10.5$, 1H), 2.17 (br s, 1H), 2.05−1.75 (m, 4H), 1.68 (dd, $J = 10.5$, $J = 1.7$, 1H), 1.44−1.32 (m, 1H), 1.06 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 218.8, 58.6, 48.5, 44.6, 41.2, 30.1, 25.7, 22.9, 21.6, 5.9 ppm.

(1*R*)-10-Hydroxycamphor [10a(OH)]. A solution of **9a** (152 mg, 1.0 mmol) and 599 mg of *m*-CPBA (57−86% purity) in 15 mL of CH_2Cl_2 was stirred at room temperature for 24 h (the reaction time was monitored by GLC). Finally, the reaction mixture was treated with 15 mL of saturated sodium hydrogensulfite solution and extracted with CH_2Cl_2. The organic layer was washed with saturated sodium hydrogencarbonate solution and with brine, and dried over anhydrous magnesium sulfate. After filtration and solvent evaporation, the residue was purified by column chromatography (silica gel, CH_2Cl_2/ether 80:20) to yield pure **10a(OH)**[26] (131 mg, 78% yield).

(1*R*)-10-Hydroxyfenchone [10b(OH)]. Following the above-described procedure for the preparation of **10a(OH)**, 152 mg (1.0 mmol) of **9b** was reacted with *m*-CPBA with a reaction time of 24 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(OH)**], the obtained residue was purified by column chromatography (silica gel, CH_2Cl_2/ether 80:20) to yield pure **10b(OH)**[30,32] (138 mg, 82% yield).

(1*S*)-10-[(*p*-Nitrophenyl)sulfanyl]camphor [10a(*p*-NO_2-C_6H_4-S)]. Over a solution of **9a** (152 mg, 1.0 mmol) in 15 mL of dry CH_2Cl_2, under argon atmosphere, was added *p*-nitrobenzenesulfenyl chloride (568 mg, 3.0 mmol). The reaction mixture was stirred at room temperature for 24 h (the reaction time was monitored by GLC). Finally, the reaction mixture was poured into 20 mL of saturated sodium hydrogencarbonate solution and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration and solvent evaporation, the residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 80:20) to yield pure **[10a(*p*-NO_2-C_6H_4-S)]** (213 mg, 70% yield) as a pale-brown solid: Mp >100 °C dec. $[\alpha]^{20}_D$ +7 (0,22, CH_2Cl_2). FTIR (CCl_4) ν 2962, 1745, 1583, 1520, 1338 cm^{-1}. MS *m*/*z* 305 [M$^{+\bullet}$(^{32}S), 25], 307 [M$^{+\bullet}$(^{34}S), 1]. HRMS *m*/*z* 305.1090 [calcd for $C_{16}H_{19}NO_3S$ (^{32}S) 305.1086]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.13 (AA′XX′, 2H), 7.37 (AA′XX′, 2H), 3.37 (AB, $J = 12.6$, 1H), 2.99 (AB, $J = 12.6$, 1H), 2.52−2.37 (dm, $J = 18.5$, 1H), 2.17−1.94 (m, 3H), 1.94 (d, $J = 18.5$, 1H), 1.62−1.35 (m, 2H), 1.21 (s, 3H), 0.98 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 216.4, 148.6, 145.0, 126.1 (two signals), 123.9 (two signals), 60.4, 48.0, 43.5, 43.0, 29.2, 26.9, 26.7, 20.3, 20.2 ppm.

(1*S*)-10-[(*p*-Nitrophenyl)sulfanyl]fenchone [10b(*p*-NO_2-C_6H_4-S)]. Following the above-described procedure for the preparation of **10a(*p*-NO_2-C_6H_4-S)**, 152 mg (1.0 mmol) of **9b** was reacted with *p*-nitrobenzenesulfenyl chloride with a reaction time of 24 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(*p*-NO_2-C_6H_4-S)**], the obtained residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 80:20) to yield pure **10b(*p*-NO_2-C_6H_4-S)**[30] (290 mg, 95% yield) as a pale-yellow liquid: $[\alpha]^{20}_D$ −4[30] (0,51, CH_2Cl_2). FTIR (CCl_4) ν 2970, 1743, 1603, 1581, 1518, 1340 cm^{-1}. MS *m*/*z* 151 (M$^{+\bullet}$−SAr, 66). HRMS *m*/*z* 305.1089 [calcd for $C_{16}H_{19}NO_3S$ (^{32}S) 305.1086]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.11 (AA′XX′, 2H), 7.37 (AA′XX′, 2H), 3.40 (AB, $J = 13.1$, 1H), 3.25 (AB, $J = 13.1$, 1H), 2.18 (br s, 1H), 1.98−1.71 (m, 4H), 1.65 (dd, $J = 10.5$, $J = 1.9$, 1H), 1.49−1.35 (m, 1H), 1.08 (s, 3H), 1.07 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 220.5, 148.0, 145.1, 126.4 (two signals), 124.5 (two signals), 58.0, 47.7, 45.2, 38.9, 32.0, 29.5, 24.7, 23.1, 21.5 ppm.

(1*S*)-10-(Phenylselanyl)camphor [10a(C_6H_5-Se)]. Following the above-described procedure for the preparation of **10a(*p*-NO_2-C_6H_4-S)**, 152 mg (1.0 mmol) of **9a** was reacted with benzeneselenyl chloride instead of *p*-nitrobenzenesulfenyl chloride with a reaction time of 24 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(*p*-NO_2-C_6H_4-S)**], the obtained residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 80:20) to yield pure **10a(C_6H_5-Se)** (252 mg, 82% yield) as a pale-brown solid: Mp 36−38 °C. $[\alpha]^{20}_D$ −52 (0.22, CH_2Cl_2). FTIR (CCl_4) ν 3055, 2959, 1742, 1578, 1477, 1389 cm^{-1}. MS *m*/*z* 304 [M$^{+\bullet}$(^{76}Se), 4], 305 [M$^{+\bullet}$(^{77}Se), 4], 306 [M$^{+\bullet}$(^{78}Se), 12], 308 [M$^{+\bullet}$(^{80}Se), 24], 310 [M$^{+\bullet}$(^{82}Se), 4]. HRMS 308.0679 [calcd for $C_{16}H_{20}OSe$ (^{80}Se) 308.0679]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56−7.51 (m, 2H), 7.26−7.22 (m, 3H), 3.26 (AB, $J = 12.2$, 1H), 2.78 (AB, $J = 12.2$, 1H), 2.40 (dm, $J = 18.4$, 1H), 2.12−2.09 (m, 1H), 2.00−1.87 (m, 2H), 1.89 (d, $J = 18.3$, 1H), 1.69 (dd, $J = 9.0$, $J = 9.0$, 1H), 1.38 (dd, $J = 9.0$, $J = 9.0$, 1H), 1.02 (s, 3H), 0.91 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 217.3, 132.6, 132.4 (two signals), 129.0 (two signals), 126.6, 61.3, 48.1, 43.5, 43.1, 27.8, 26.8, 25.3, 20.1, 20.0 ppm.

(1*S*)-10-(Phenylselanyl)fenchone [10b(C_6H_5-Se)]. Following the above-described procedure for the preparation of **10a(*p*-NO_2-C_6H_4-S)**, 152 mg (1.0 mmol) of **9b** was reacted with benzeneselenyl chloride instead of *p*-nitrobenzenesulfenyl chloride with a reaction time of 24 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(*p*-NO_2-C_6H_4-S)**], the obtained residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2 80:20) to yield pure **10b(C_6H_5-Se)**[30] (270 mg, 88% yield) as a yellow liquid. $[\alpha]^{20}_D$ +9[30] (0.22, CH_2Cl_2). FTIR (film) ν 3059, 2968, 1742, 1580, 1477, 1383 cm^{-1}. MS *m*/*z* 304 [M$^{+\bullet}$(^{76}Se), 2], 305 [M$^{+\bullet}$(^{77}Se), 2], 306 [M$^{+\bullet}$(^{78}Se), 7], 308

[$M^{+\bullet}$(^{80}Se), 14], 310 [$M^{+\bullet}$(^{82}Se), 2]. HRMS 308.0674 [calcd for $C_{16}H_{20}OSe$ (^{80}Se) 308.0679]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.54−7.49 (m, 2H), 7.27−7.21 (m, 3H), 3.28 (AB, J = 12.9, 1H), 3.11 (AB, J = 12.9, 1H), 2.13 (br s, 1H), 1.93−1.66 (m, 4H), 1.57 (dd, J = 10.5, J = 1.7, 1H), 1.41−1.25 (m, 1H), 1.05 (s, 3H), 1.04 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 220.0, 132.3 (two signals), 131.6, 129.0 (two signals), 126.7, 59.1, 47.8, 45.0, 39.5, 30.1, 28.2, 24.9, 23.0, 21.5 ppm.

(1*S*)-10-[(Dimethylamino)methyl]camphor [10a(CH_2-NMe_2)]. A dispersion of 152 mg of **9a** (1.0 mmol) and 204 mg of Eschemoser's salt (1.1 mmol) in 30 mL of dry $CHCl_3$ was stirred at refluxing temperature under argon atmosphere for 36 h. After extraction, washing, drying, filtration, and solvent elimination [vide supra in the preparation of **10a(Br)**], the obtained residue was purified by column chromatography (neutral aluminum oxide, CH_2Cl_2/ethyl acetate, 50:50) to yield pure **10a(CH_2NMe_2)** (205 mg, 98% yield) as a colorless oil. $[\alpha]^{20}_D$ +8 (0.95, $CHCl_3$). FTIR (film) ν 2960, 1736 cm^{-1}. MS m/z 209 ($M^{+\bullet}$, 3). HRMS 209.1787 (calcd for $C_{13}H_{23}NO$ 209.1780). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.80 (td, J = 11.8, J = 4.9, 1H), 2.36 (td, J = 11.8, J = 4.9, 1H), 2.33 (s, 6H), 2.03 (dd, J = 3.3, J = 3.3, 1H), 2.00−1.86 (m, 1H), 1.78 (d, J = 18.1, 1H), 1.80−1.25 (m, 6H), 0.94 (s, 3H), 0.85 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 219.0, 59.1, 55.1, 47.6, 45.0 (two signals), 43.4, 43.2, 27.0, 26.7, 23.4, 20.2, 19.6 ppm.

(1*R*)-10-[(Dimethylamino)methyl]fenchone [10b(CH_2-NMe_2)]. Following the above-described procedure for the preparation of **10a(CH_2NMe_2)**, 152 mg (1.0 mmol) of **9b** was reacted with a reaction time of 36 h. After extraction, washing, drying, filtration, solvent elimination, and purification by column chromatography [vide supra in the preparation of **10a-(CH_2NMe_2)**], pure **10b(CH_2NMe_2)**[30] (205 mg, 98% yield) was obtained as a colorless oil. $[\alpha]^{20}_D$ −20.1[30] (1.1, $CHCl_3$). FTIR (film) ν 2947, 1738 cm^{-1}. MS m/z 181 ($M^{+\bullet}$ − 28, 3). HRMS 209.1779 (calcd for $C_{13}H_{23}NO$ 209.1780). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.49−2.19 (m, 2H), 2.24 (s, 6H), 2.08 (m, 1H), 1.93−1.53 (m, 6H), 1.39 (dd, J = 10.4, J = 1.8, 1H), 1.33−1.19 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 218.6, 56.6, 55.9, 47.4, 45.1 (two signals), 44.9, 38.4, 30.2, 26.7, 24.1, 22.8, 21.3 ppm.

(1*R*)-3,3-Dimethyl-1-methoxy-2-methylenenorbornane [16a(OMe)]. Over a solution of **9a** (152 mg, 1.0 mmol) in 10 mL of dry THF at −78 °C under argon atmosphere was added dropwise 0.9 mL of butyllithium 1.6 M in hexane (1.1 mmol) via syringe. After that, the reaction mixture was allowed to warm to room temperature and stirred for 30 min. Then, 710 mg (5.0 mmol) of methyl iodide was added dropwise via syringe at room temperature. When the addition was complete, the mixture was refluxed for 3 h (the reaction progress was monitored by GLC). Finally, the reaction was cooled to 0 °C, carefully hydrolyzed with 10 mL of saturated ammonium chloride solution, and extracted with ether. The organic layer was washed with saturated sodium hydrogencarbonate solution and with brine, and dried over anhydrous magnesium sulfate. After filtration and solvent evaporation, the residue was purified by column chromatography (silica gel, hexane), to yield pure **16a(OMe)** (149 mg, 90% yield) as a colorless liquid: $[\alpha]^{20}_D$ −16 (0.71, CH_2Cl_2). FTIR (film) ν 3072, 2960, 1662, 1306, 1030 cm^{-1}. MS m/z 166 ($M^{+\bullet}$, 13). HRMS 166.1354 (calcd for $C_{11}H_{18}O$ 166.1358). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.81 (s, 1H), 4.68 (s, 1H), 3.32 (s, 3H), 1.94−1.54 (m, 5H), 1.44 (dd, J = 9.2, J = 1.4, 1H), 1.42−1.26 (m, 1H), 1.07 (s, 3H), 1.03 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.9, 99.0, 90.2, 53.1, 43.9, 42.0, 37.5, 32.3, 29.1, 26.3, 24.5 ppm.

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