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Straightforward synthesis of (1*S*)-10-dimethylaminomethylcamphor: an enantiospecific model procedure to C10–C-substituted camphor-derived chiral sources

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Abstract—Enantiopure 3,3-dimethyl-2-methylenenorbornan-1-ol, readily obtained from commercially available camphor, is able to react with Eschenmoser's salt under very soft reaction conditions. This reaction constitutes the first example in which a non-mesomerically activated olefin easily adds the Eschenmoser's salt. The addition takes place regiospecifically and it is followed by an enantiospecific Wagner–Meerwein rearrangement of the norbornane skeleton to afford enantiopure 10-dimethylaminomethylcamphor, an interesting chiral δ-amino ketone, with excellent yield. The obtained amino ketone is a key intermediate to new valuable C10–C-substituted camphor-derived chiral sources.

C10-Substituted camphor derivatives are an important class of chiral sources which have been widely used as chiral auxiliaries (e.g. Oppolzer's sultame **1**), chiral reagents (e.g. Davis' oxaziridine **2**), chiral resolving agents (e.g. 10-camphorsulfonic acid **3**) or chiral catalysts (e.g. Yus' sulfonamide **4**) in many asymmetric transformations (Fig. 1).[1] Most of the described C10-substituted camhor-derived chiral sources are C10-heteroatomically subtituted, such as C10-S, C10-Se, C10-O, C10-N, C10-halogen, C10-P or C10-Te, C10-S is the most frequent substitution.[2] Oppositely, examples of C10–C-substituted camphor-derived chiral sources are practically inexistent. This is due to the fact that most of the described C10-substituted camphors are prepared from **3**, the first obtained C10-substituted camphor, or by nucleophilic bromine-substitution in 10-bromocamphor (a key intermediate to C10-heteroaromatic-substituted camphors, also obtained, up to recent days, from **3**).[2]

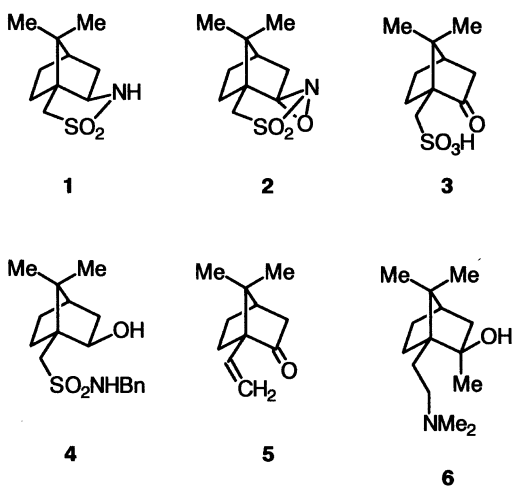

Figure 1. Some selected C10-substituted camphors.

Nevertheless, some interesting C10–C-substituted camphors have been prepared and used as valuable chiral sources (e.g. 10-methylenecamphor **5** as starting intermediate in the Paquette's approach to anticancer taxol,[3] or β-amino alcohol **6** as chiral catalyst for the asymmetric addition of diethylzinc to benzaldehyde).[4]

Related to the preparation of enantiopure C10-substituted camphors, we have recently reported that (1*R*)-3,3-dimethyl-2-methylenenorbornan-1-ol **7**, which is straightforwardly obtained from commercially available natural (1*R*)-camphor,[5] is a key intermediate to these kind of camphor derivatives.[6] Thus, the treatment of **7** with electrophiles able to react easily with carbon–carbon double bonds, such as *N*-bromosuccin-

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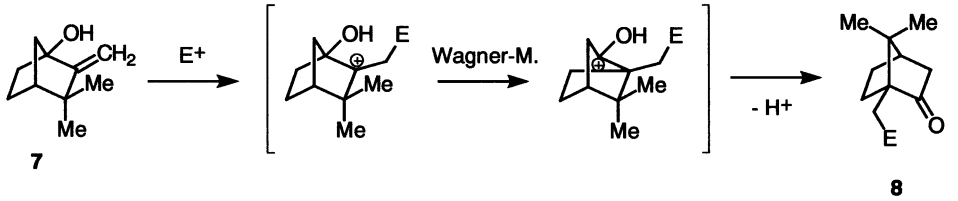
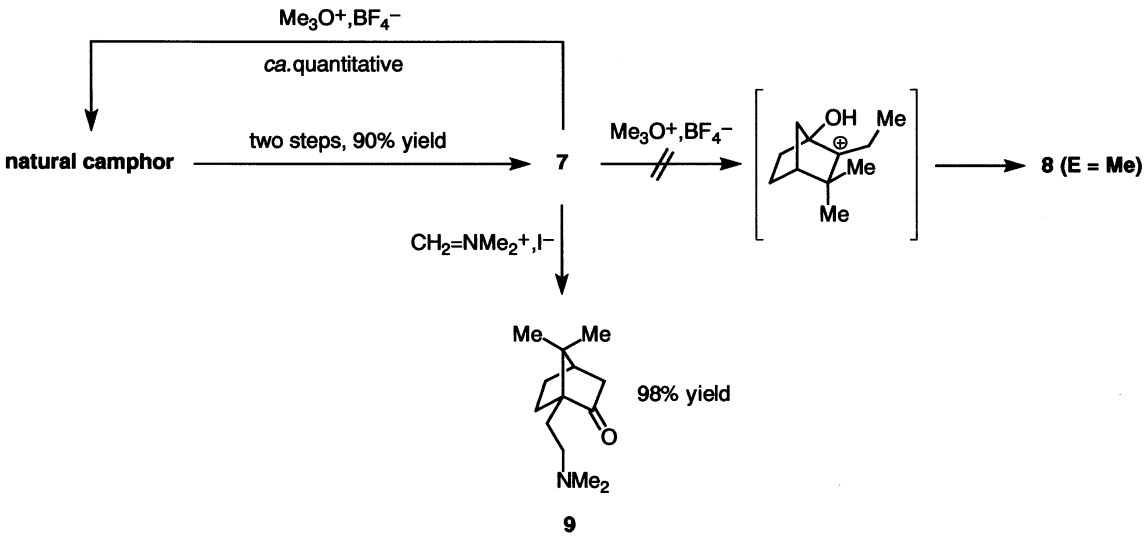


Scheme 1. Key tandem electrophilic carbon–carbon double-bond addition—Wagner–Meerwein rearrangement.



Scheme 2. Two different reaction pathways of **7** with carbon electrophiles (Meerwein's salt versus Eschenmoser's salt).

imide, *m*-CPBA, arylsulfenyl halides or arylselenyl halides ($E^+ = Br^+$, OH^+, ArS^+ or $ArSe^+$), takes place with a tandem of regiospecific carbon–carbon double-bond addition—Wagner–Meerwein rearrangement to give straightforwardly the corresponding 10-bromocamphor (**8**, E = Br), 10-hydroxycamphor (**8**, E = OH), 10-arylsulfanylcamphor (E = ArS) and 10-arylselanylcamphor (E = ArSe) (Scheme 1).[6]

As a result of this, we attempted to obtain 10-methylcamphor (**8**, E = Me), a simple C10–C-substituted camphor, by reacting **7** with the stabilized carbon–electrophile Meerwein's salt (trimethyloxonium tetrafluoroborate, $Me_3O^+BF_4^-$).[7] Nevertheless, when **7** is reacted with Meerwein's salt, only camphor was the obtained reaction product (Scheme 2).[7] This result can be explained due to the favored reaction of the hydroxy group of **7** with the hard Lewis acid Meerwein's salt.[8]

We have now found that the treatment of **7** with the softer Lewis acid Eschenmoser's salt takes place with carbon–carbon double-bond addition and Wagner–Meerwein rearrangement to give enantiopure (1*S*)-10-dimethylaminomethylcamphor **9** as the only camphor-derived product with ca. quantitative yield (Scheme 2). The reaction occurs under mild reaction conditions (refluxing $CHCl_3$ solution) according to the mechanism described in Scheme 1.[9]

Mechanistically, the described reaction constituted the first example in which Eschenmoser's salt reacts with a non-mesomerically activated olefin, but with a homoconjugated one (note activation of the carbon–carbon double bond by homoconjugation with the bridgehead hydroxy group in **7**).[10]

In summary, the reaction of the enantiopure camphor-derived 2-methylenenorbornan-1-ol **7** with Eschenmoser's salt yields the corresponding 10-aminomethylcamphor **9**, a C10–C-subtituted camphor. The reaction takes place enantiospecifically, constituting a straightforward model procedure to other C10–C-substituted camphor-derived chiral sources from readily available camphor (i.e. the reaction of **7** with other iminium salts). Moreover, described enantiopure camphor-derived β-amino ketone **9** is a key intermediate to enantiopure β-amino alcohols of the type of **6** (e.g. via nucleophilic addition to the carbonyl group), which could be used as valuable catalysts for the asymmetric addition of diethylzinc to aldehydes.[4a,b]

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References

1. As a review, see: (a) Oppolzer, W. *Tetrahedron* **1987**, 1969. Some selected recent examples are: (b) Mizojiri, R.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2666; (c) Cermak, D. M.; Du, Y.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 388; (d) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176; (e) Ponsinet, R.; Chassaing, G.; Vaissermann, J.; Lavielle, S. *Eur. J. Org. Chem.* **2000**, 83; (f) Kaptein, B.; Elsenberg, H.; Grimbergen, R. F. P.; Broxterman, Q. B.; Hulshof, L. A.; Pouwer, K. L.; Vries, T. R. *Tetrahedron: Asymmetry* **2000**, *11*, 1343; (g) Sasaki, H.; Carreira, E. M. *Synthesis* **2000**, 135; (h) Yoshioka, R.; Hiramatsu, H.; Okamura, K.; Tsujioka, I.; Yamada, S.-I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2115; (i) Wang, C.-C.; Huang, H.-C.; Lee, L. F.; Reitz, D. B. *J. Org. Chem.* **2000**, *65*, 2711; (j) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1629; (k) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953.
2. Referred to C10-S, see: (a) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927; (b) Manzi, M.; Minetti, P.; Moretti, G.; Tinti, M. O.; De Angelis, F. *J. Org. Chem.* **2000**, *65*, 6766; (c) Nakano, H.; Okuyama, Y.; Yanagida, M.; Hongo, H. *J. Org. Chem.* **2001**, *66*, 620; (d) Aggarwald, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430; see also Ref. 5. Referred to C10-Se, see: (e) Takahashi, T.; Nakao, N.; Koizumi, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3293; (f) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1; see also Ref. 10c. Referred to C10-0, see: (g) Dallacker, F.; Alroggen, I.; Krings, H.; Laurs, B.; Lipp, M. *Liebigs Ann. Chem.* **1961**, *647*, 23; (h) Ikota, N.; Sakai, H.; Shibata, H.; Koga, K. *Chem. Pharm. Bull.* **1986**, *34*, 1050; (i) Jingen, D.; Yaozong, J.; Guilan, L.; Lanjun, W.; Aiqiao, M. *Synthesis* **1991**, 963; (j) Ahn, K. H.; Lee, S.; Lim, A. *J. Org. Chem.* **1992**, *57*, 5065; (k) Ahn, K. H.; Lim, A.; Lee, S. *Tetrahedron: Asymmetry* **1993**, *4*, 2435; (l) 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; (m) Gaisina, I. N.; Komissarova, N. G.; Selezneva, N. K.; Abutkov, A. V.; Spirikhin, L. V.; Muslukhov, R. R.; Miftakhov, M. S. *Zh. Org. Khim.* **1999**, *35*, 1025; see also Ref. 10b. Referred to C10-N, see: (n) Schenone, P.; Tasca, A.; Bignardi, G.; Mosti, L. *Eur. J. Med. Chem.—Chimica Therapeutica* **1975**, *10*, 412; (j) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729; (o) Lin, C.-H.; Yang, K. S.; Pan, J.-F.; Chen, K. *Tetrahedron Lett.* **2000**, *41*, 6815; (p) Yang, K.-S.; Chen, K. *J. Org. Chem.* **2001**, *66*, 1676; (p) Chapuis, C.; Kucharska, A.; Jurczak, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4581. Referred to C10-halogen, see: (q) Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3802; (r) Ferguson, C. G.; Money, T.; Pontillo, J.; Whitelaw, P. D. M.; Wong, M. K. C. *Tetrahedron* **1996**, *52*, 14661; see also Refs. 10a and 10g. Referred to C10-P, see: (s) Komarov, I. V.; Gorichko, M. V.; Kornilov, M. *Tetrahedron: Asymmetry* **1997**, *8*, 435; (t) Thorsten, S.; Laschat, S.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2000**, 4119. Referred to C10-Te, see: (u) Zhang, J.; Saito, S.; Koizumi, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3357; (v) Zhang, J.; Saito, S.; Koizumi, T. *J. Org. Chem.* **1998**, *63*, 5423.
3. (a) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203; (b) Paquette, L. A.; Zhao, M.; Montgomery, F.; Zheng, Q.; Wang, T. Z.; Elmore, S.; Combrink, K.; Wang, H.-L.; Bailey, S.; Su, Z. *Pure Appl. Chem.* **1998**, *70*, 1449.
4. (a) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2971; (b) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4127; (c) Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2000**, *41*, 4587.
5. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Ruano Franco, C.; Soto Salvador, J.; Subramanian, L. R.; Hanack, M. *Synthesis* **1987**, 321. See also Ref. 10a and references cited therein.
6. (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.
7. Over a solution of alcohol **7** in CH_2Cl_2 under argon atmosphere was added Meerwein's salt (1 mol equiv.), and then stirred at room temperature for 12 h. After usual work up camphor was obtained in ca. quantitative yield.
8. Hard-acid Meerwein's salt must react with the hard-base hydroxy group, according to the HSAB principle (Ho, T.-L. *Tetrahedron* **1985**, *41*, 1), forming corresponding non-isolated 1-methoxy-2-methylenenorbornane, which undergoes favored Wagner–Meerwein rearrangement to camphor by proton-addition (tetrafluoroboric acid) to the carbon–carbon double bond.
9. A dispersion of alcohol **7** and Eschenmoser's salt (1.1 mol equiv.) in $CHCl_3$ was stirred at refluxing temperature under argon atmosphere for 36 h. After usual work up, amino ketone **9** was obtained in 98% yield as colorless oil. $[\alpha]_D^{20}$ +7.68 (0.95, $CHCl_3$). MS m/z 209 ($M^{+\bullet}$, 3), 58 (100). IR (film) 1736 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) 2.80 (td, $J=11.8$ Hz, $J=4.9$ Hz, 1H), 2.36 (td, $J=11.8$ Hz, $J=4.9$ Hz, 1H), 2.35–2.22 (m, 1H), 2.33 (s, 6H), 2.03 (dd, $J=3.3$ Hz, $J=3.3$ Hz, 1H), 2.00–1.86 (m, 1H), 1.78 (d, $J=18.1$ Hz, 1H), 1.80–1.25 (m, 5H), 0.94 (s, 3H), 0.85 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) 219.0, 59.1, 55.1, 47.6, 45.0, 43.4, 43.2, 27.0, 26.7, 23.4, 20.2, 19.6 ppm.
10. Some electronically (mesomerically) activated olefins such as enamines, pyrroles, porphyrins and chlorins, as well as their vinilogous are able to add Eschenmoser's salt: (a) Barnett, C. J.; Copley-Merriman, C. R.; Maki, J. *J. Org. Chem.* **1989**, *54*, 4795; (b) Mitch, C. H.; Zimmeramn, D. M.; Snoddy, J. D.; Reel, J. K.; Cantrell, B. E. *J. Org. Chem.* **1991**, *56*, 1660; (c) Pandey, R. K.; Shiau, F.-Y.; Smith, N. W.; Douherty, T. J.; Smith, K. M. *J. Chem. Soc., Chem. Commun.* **1991**, 1637; (d) Pandey, R. K.; Shiau, F.-Y.; Smith, N. W.; Douherty, T. J.; Smith, K. M. *Tetrahedron* **1992**, 48, 7591; (e) Nguyen, L. T.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1996**, 61, 998; (f) Xie, H.; Lee, D. A.; Wallace, D. M.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1996**, *61*, 8508; (g) Bennasar, M. L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597; (h) Kobayashi, K.; Matsumoto, T.; Irisawa, S.; Yoneda, K.; Morikawa, O.; Konishi, H. *Heterocycles* **2001**, *55*, 973.