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A novel route to enantiopure cyclopentene carboxylic acids based on 3-*endo*-bromocamphor

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Abstract—A novel four-step synthetic route to enantiopure cyclopentene carboxylic acids starting from commercially available 3-*endo*-bromocamphor is described. The synthesis is straightforward and practical. The key transformations involve firstly, an enantiospecific Wagner–Meerwein rearrangement of a bromocamphor derived cyanohydrin, and secondly the regiospecific C-(1)–C-(2) bond scission of a 7-bromonorbornan-2-one.

There is a great deal of current interest in new synthetic routes to enantiopure substituted cyclopentanoids, which is due to the fact that many natural products with interesting biological and medicinal activities present a chiral five-membered carbocycle as their basic moiety (e.g. prostaglandins, jasmonoids, steroids, gibberellins, cyclitols, etc.).[1] Among the variety of naturally occurring substituted cyclopentanoids, homochiral cyclopentane- and cyclopentene carboxylic acids (and their acid derivatives such as esters, nitriles, alcohols, etc.) have special significance in natural product chemistry (Fig. 1).[1] As such, the establishment of new efficient synthetic routes to enantiopure cyclopentene carboxylic acids of the type **1** is of great interest.[1]

Most of the described synthetic routes to enantiopure cyclopentanoid derivatives are based on the regiospecific fragmentation of a key enantiopure functionalized norbornane intermediate.[2] Unfortunately, this key norbornane is usually built up through an asymmetric Diels–Alder reaction, which often requires the use of a chiral auxiliary, and can reduce the efficiency of the synthesis (depending on the e.e. obtained in the cycloaddition step).[3] This problem can be solved if the norbornane intermediate is obtained by functionalization of the naturally occurring camphor skeleton, which, advantageously, can be achieved with high diastereomeric excesses due to both rigidity and steric factors inherent to the camphor framework.[1g]

Herein, we describe a novel route to the interesting enantiopure cyclopentene carboxylic acids **7** and **8** starting from commercial 3-*endo*-bromocamphor **2** (Scheme 1). The first step involves the preparation of the diasteromeric cyanohydrins **3** and **4** from (1*R*)-3-*endo*-bromocamphor **2** by a standard procedure previously described by us.[4,5] Separation of both diastereomeric cyanohydrins **3** and **4** is required, since only the *exo*-hydroxy cyanohydrin **4** is able to undergo reaction with triflic anhydride[6] to give the 7-*anti*-bromo-2-methylenenorbornane **5**.[5,7] Methylenenorbornane **5** is subsequently ozonolyzed to give the corresponding 7-*anti*-bromonorbornan-2-one **6** in near quantitative yield.[5] Finally, a mild basic hydrolysis of **6** yields the cyclopentene cyano-acid **7** (sodium bicarbonate hydrolysis) or di-acid **8** (sodium hydroxide hydrolysis) with high yields (91% for **7** and 93% for **8**).[8] Non-reactive cyanohydrin **3** can be quantitatively hydrolyzed under mild basic conditions (10% NaOH, room temperature) to starting bromocamphor **2**, which improves the overall yield of the described synthetic procedure.

The key steps of the above described route are the enantiospecific Wagner–Meerwein rearrangement of **4** by reaction with triflic anhydride;[9] and the regiospecific C-(1)–C-(2) bond scission of 2-norbornanone **6** under basic hydrolysis, which is promoted by the presence of

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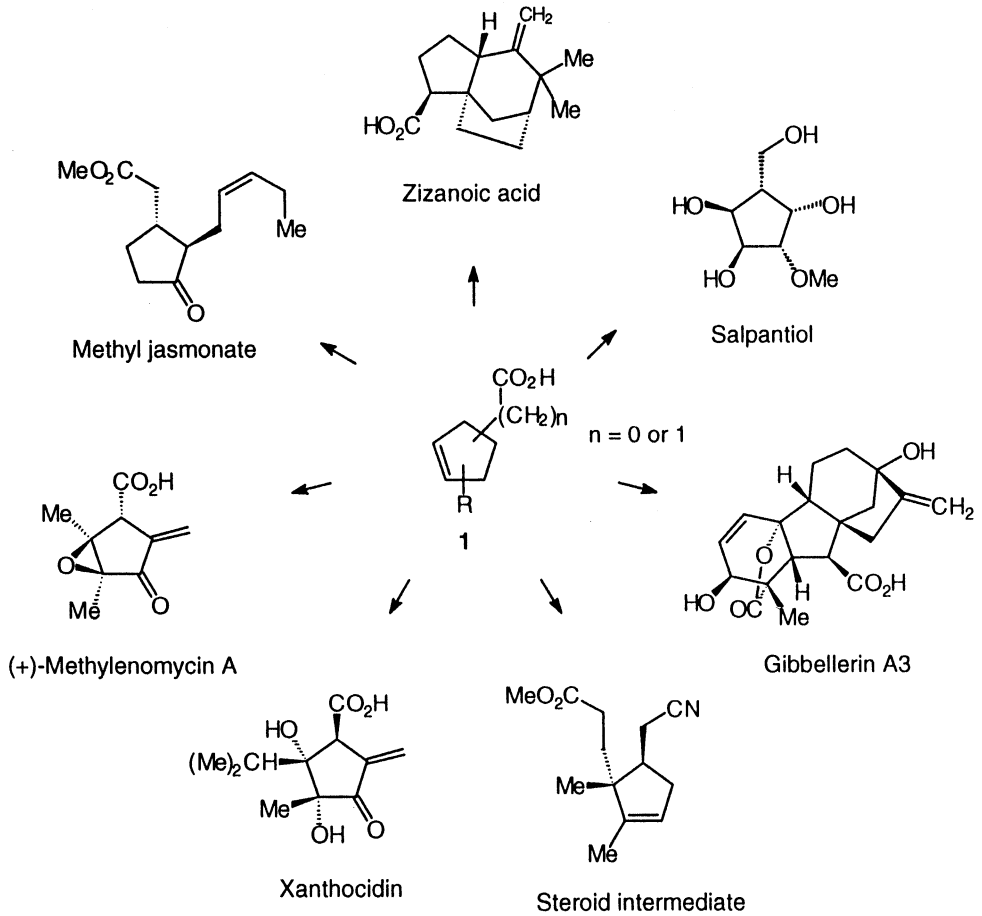
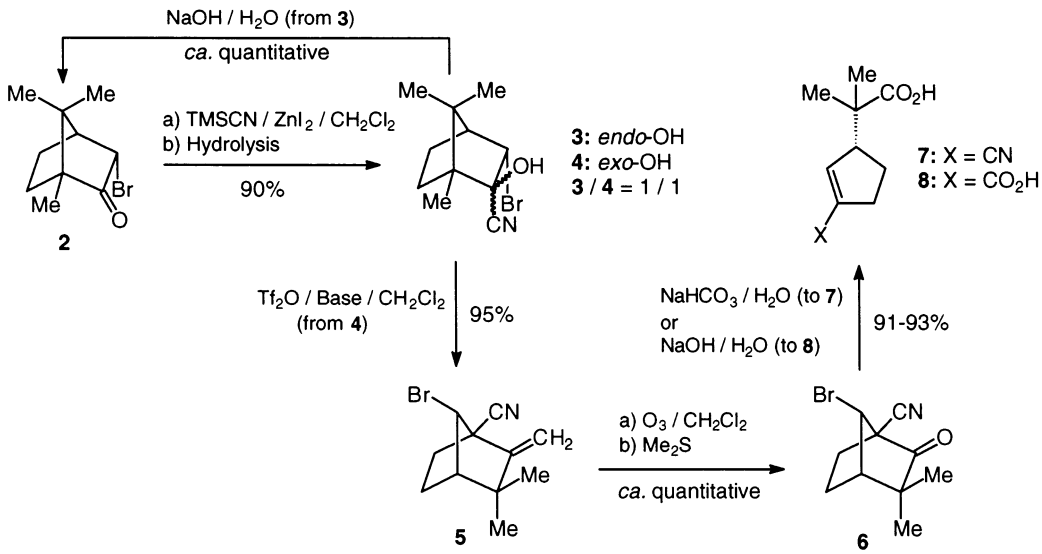


Figure 1. Some relevant natural products with chiral cyclopentanoid carboxylic acid moiety.



Scheme 1. Novel 3-*endo*-bromocamphor based route to enantiopure cyclopentene carboxylic acids.

the bromine atom attached to the C-(7) position (Scheme 2).[10]

In conclusion, a new route to interesting enantiopure cyclopentene carboxylic acid intermediates starting from readily available 3-*endo*-bromocamphor has been described. The straightforward preparation of the described cyclopentenes establishes a synthetic model to other versatile enantiopure cyclopentanoids.

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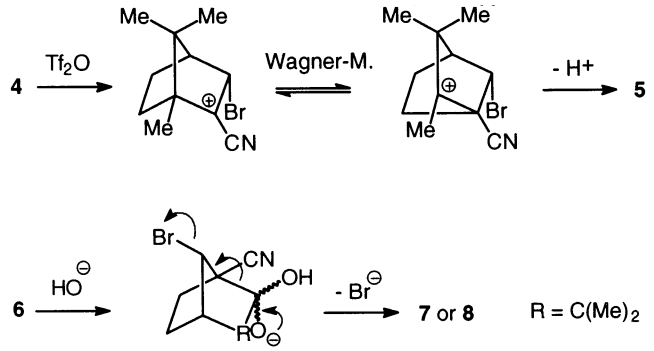

Scheme 2. Key synthetic steps of the described route.

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1. For example, see: (a) Hanessian, S. In *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983; (b) Paquette, L. A.; Doherty, A. M. In *Poliquinane Chemistry: Syntheses and Reactions*; Springer Verlag: Berlin, 1987; (c) Money, T.; Atta-ur-Rahman In *Studies in Natural Products Chemistry*; Elsevier: Amsterdam, 1989; Vol. 4; (d) Ho, H.-T. In *Enantioselective Synthesis: Natural Products from Chiral Terpenes;* John Wiley and Sons: New York, 1992; (e) Koskinen, A. In *Asymmetric Synthesis of Natural Products;* John Wiley and Sons: Chichester, 1998; (f) Mann, J.; Davidson, R. S.; Hobbs, J. B.; Banthorpe, D. V.; Harbone, J. B. In *Natural Products: their Chemistry and Biological Significance*; Addison Wesley Longman: Essex, UK 1998; (g) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.
2. Some examples are related to C-(1)–C-(2) scission: (a) Stevens, R. V.; Gaeta, F. C. A.; Lawrence, D. S. *J. Am Chem. Soc.* **1983**, *105*, 7713; (b) Gream, G. E.; Wege, D.; Mular, M. *Aust. J. Chem.* **1974**, *27*, 567; (c) Liu, H. J.; Chan, W. H. *Can. J. Chem.* **1979**, *57*, 708; (d) Liu, H. J.; Chan, W. H.; *Can. J. Chem.* **1982**, *60*, 1081; (e) Hutchinson, J. H.; Piper, S. E.; Money, T. *J. Chem. Soc., Chem. Commun.* **1984**, 455; (f) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Díaz Oliva, C.; Maichle, C.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1994**, *5*, 949; (g) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2177; (h) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S. Martínez Ruiz, P.; García Álvarez, P. P. *Tetrahedron: Asymmetry* **1997**, *8*, 849; (i) Nagata, H.; Taniguchi, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **1997**, *8*, 2679; (j) Metha, G.; Mohal, N. *Tetrahedron Lett.* **1999**, *40*, 5791 and 5795; related to C2–C3 scission; (k) Okada, K.; Mukai, T. *Tetrahedon Lett.* **1980**, *21*, 359; (l) Shibuya, H.; Fukioka, H.; Yamamoto, Y. *Chem. Pharm. Bull.* **1982**, *30*, 1280; (m) Linz, G.; Weetman, J.; Hady, A.; Helmchem, G. *Tetrahedron Lett.* **1989**, *30*, 5599; (n) Ikeda, I.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1995**, 453; (o) García Martínez, A.; Teso Vilar, E.; Osío Barcina, J.; Manrique Alonso, J.; Rodríguez Herrero, M. E.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1992**, *33*, 607.
3. As examples, see Refs. 1e and 2j,m,n.
4. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; González-Fleitas de Diego, J. M.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1994**, *5*, 1599. Cyanohydrins **3** and **4** are easily separated by elution chromatography (silica gel/CH_2Cl_2).
5. The structures of **3**–**6** were confirmed by MS, IR and NMR spectra.
6. Probably due to steric hinder over the hydroxy group exerted by *endo*-bromine at C-(3).
7. Triflic anhydride treatment is realized as described in Ref. 4.
8. A dispersion of norbornanone **6** in saturated $NaHCO_3$ solution (or 10% NaOH solution) was stirred at room temperature for 6 h. The mixture was acidified with diluted HCl and after usual work up, **7** (or **8**) is obtained. Compound **7**: White solid, mp 148.4–149.0°C. $[\alpha]_D^{20}$+69.6 (1.40, CH_2Cl_2). IR ($CHCl_3$) ν 2978, 2222, 1701, 1369 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 11.10 (br s, 1H), 6.60 (c, J=2.2, 1H), 3.23 (m, 1H), 2.60 (m, 2H), 2.14 (m, 1H), 1.75 (m, 1H), 1.21 (s, 3H), 1.17 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 183.2, 149.1, 116.4, 116.0, 54.4, 44.9, 34.0, 25.2, 22.6, 22.3 ppm.
   Compound **8**: white solid (decomposes near 110°C). $[\alpha]_D^{20}$+30.1 (1.84, CH_2Cl_2). IR ($CHCl_3$) ν 2976, 1693, cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 10.61 (br s, 2H), 6.85 (d, J=2.0, 1H), 3.24 (m, 1H), 2.56 (m, 2H), 2.12 (m, 1H), 1.75 (m, 1H), 1.21 (s, 3H), 1.17 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 183.9, 170.7, 146.6, 137.2, 54.4, 45.1, 30.8, 25.7, 22.8, 22.3 ppm.
9. A destabilized α-cyano-substituted 2-norbornyl carbocation (as a tight ion pair) can be postulated as intermediate: (a) Kirmse, W.; Goer, B. *J. Am. Chem. Soc.* **1990**, *112*, 4556; (b) Della, E. W.; Elsey, G. M.; Skouroumounis, G. *Aust. J. Chem.* **1990**, *43*, 1231.
10. For a related process see Ref. 2j. See also: Komarov, I. V.; Gorichko, M. V.; Kornilov, M. Y. *Tetrahedron: Asymmetry* **1997**, *8*, 435.