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Synthesis of 7-*anti*-bromo-3,3-dimethyl-2-oxonorbornane-1-carboxylic acid: a new chiral source from the chiral pool

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Abstract—Enantiopure 7-*anti*-bromo-3,3-dimethyl-2-oxonorbornane-1-carboxylic acid, an interesting new chiral norbornane-1-carboxylic acid analogous to the well known chiral-source ketopinic acid, has been obtained for the first time from commercially available 3-*endo*-bromocamphor. The synthesis takes place enantiospecifically in four straightforward synthetic steps with high overall yield. The established route constitutes a model procedure for the preparation of other chiral C(7)-substituted 3,3-dimethyl-2-oxo-norbornane-1-carboxylic-acid-derived chiral sources (e.g. tridentate chiral ligands) from camphor.

Enantiopure norbornane-1-carboxylic acids and related derivatives are an interesting class of chirality transfer agents, which have been intensively used as chiral auxiliaries (e.g. diol **1a**, pirazolidinone **2a** or oxazinone **3a**),[1] chiral resolving agents (e.g. acid chloride **4a**),[2] and chiral ligands (e.g. phosphine–oxazinane **5a** or C_2-symmetric diamide **6a**)[3] in many asymmetric transformations, as well as chiral intermediates in the preparation of valuable molecules (e.g. in the synthesis of the antispasmodic amino esters **7a**)[4] (Fig. 1).

As shown in Fig. 1, and despite the interesting complementarities existing between camphor- and fenchone-derived chiral transfers,[5] all of the above chiral transfer agents are dimethyl-substituted at the C(7)-norbornane position (methano-bridge position), whereas the corresponding C(3)-dimethyl-substituted analogues have been neither obtained nor investigated. This is due to the fact that all of them are invariably obtained using the readily available commercial ketopinic acid **8a** (a camphor-derived 2-oxonorbornane-1-carboxylic acid) as the key starting material,[1–4] whereas the corresponding fenchone-derived 3,3-dimethylated carboxylic acid **8b** is not commercially available.[6]

Accordingly, the preparation of new enantiopure 2-oxonorbornane-1-carboxylic acids with different substitution patterns (i.e. with different topologies and, therefore, different chirality transfer properties) is of great interest, because it would allow the preparation of new chiral agents, analogous to those obtained from ketopinic acid.

In this communication we describe the enantiospecific preparation of a new 2-oxonorbornane-1-carboxylic acid **8c** from commercial available (1*R*)-3-*endo*-bromocamphor **9**. This novel chiral norbornane-1-carboxylic acid is an interesting analogue to the chiral-source ketopinic acid **8a** (3,3-disubstituted instead of 7,7-disubstituted), which would allow the preparation of new chiral trisubstituted-norbornanes, with different chirality transfer properties to **8a** (cf. **1a**–**6a** and **1c**–**6c** in Fig. 1).

The preparation of acid **8c** from 3-*endo*-bromocamphor **9** has been realized enantiospecifically as Scheme 1 shows. The key intermediate of our route is the 2-oxonorbornane-1-carbonitrile **11** (enantiospecifically obtained from **9** by triflic-anhydride-promoted Wagner–Meerwein rearrangement of the 3-*endo*-bromocamphor-derived cyanohydrin and subsequent ozonolysis),[7] which, upon controlled hydrolysis (3 days at 35°C) with 35% HCl,[8] yields the desired enantiopure 7-*anti*-bromo-2-oxonorbornane-1-carboxylic acid **8c** with high yield

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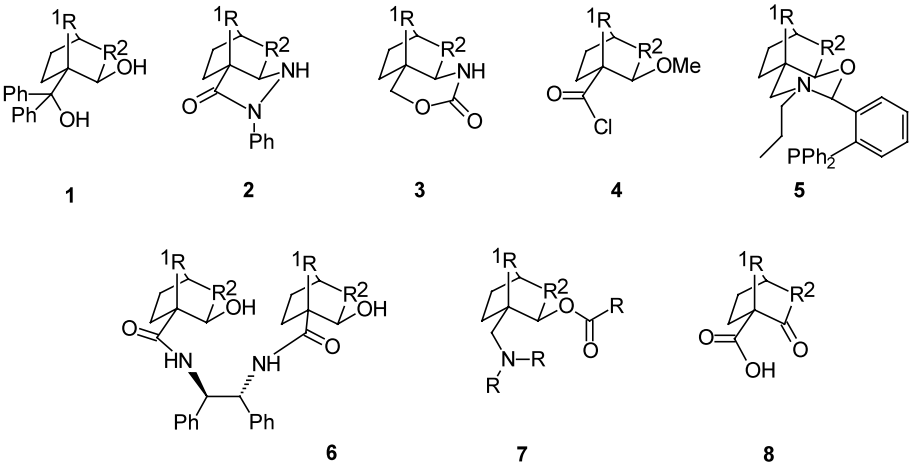
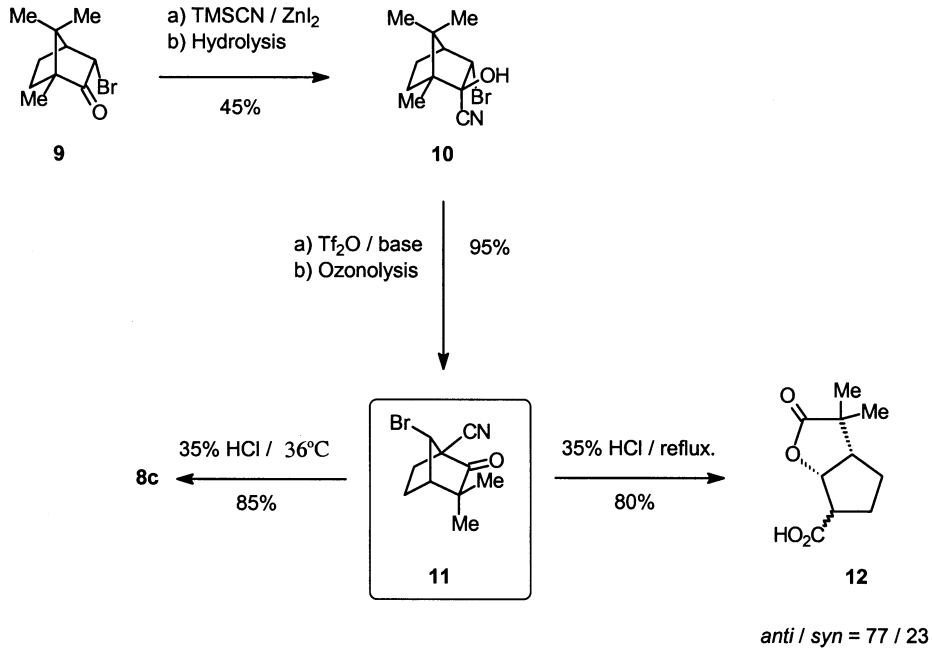


a: $R^1 = CMe_2$, $R^2 = CH_2$ // **b:** $R^1 = CH_2$, $R^2 = CMe_2$ // **c:** $R^1 = CH(anti\text{-}Br)$, $R^2 = CMe_2$

Figure 1. Some selected norbornane-1-carboxylic acid-derived chirality transfer agents.

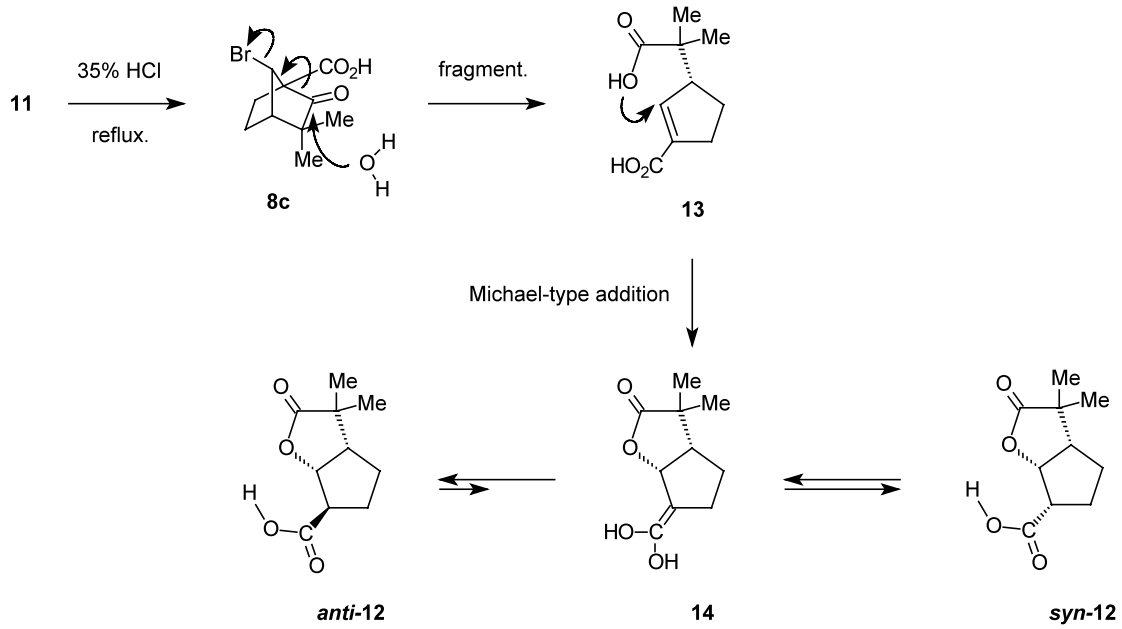


Scheme 1. Enantiospecific preparation of **8c** and **12** from 3-*endo*-bromocamphor **9**.

(Scheme 1). However, when **11** is hydrolyzed in refluxing aqueous HCl,[9] the 2-oxa-3-oxobicyclo[3.3.0]octane-8-carboxylic acid **12** is obtained instead of **8c** (Scheme 1).[10]

The striking formation of lactone **12** can be explained according to the reaction pathway indicated in Scheme 2. Thus, nucleophilic attack of water to the carbonyl group of the rigid 7-*anti*-bromonorbornane-1-carboxylic acid **8c** would take place with bromine-assisted fragmentation of the norbornane C(1)–C(2) bond,[11] to give the (undetected) Michael olefin **13**. Activated olefin **13** must undergo a stereocontrolled intramolecular Michael-type addition to give tautomer **14**, which equilibrates to the final lactone **12**, as a mixture of epimers.

In summary, a new 2-oxonorbornane-1-carboxylic acid (7-*anti*-bromo-substituted) analogous to the well known chiral source ketopinic acid has been enantiospecificially obtained from commercial 3-*endo*-bromocamphor. This norbornane-1-carboxylic acid will allow the straightforward preparation of new interesting tridentate norbornane-based chiral agents from the chiral pool. Moreover, 7-*anti*-bromo-2-oxonorbornane-1-carboxylic acid **8c** is demonstrated to be a valuable precursor of interesting cyclopentanoid intermediates (e.g. for



Scheme 2. Proposed reaction pathway from **11** to **12**.

prostaglandin-type syntheses).[10] The synthetic route to **8c** from 3-*endo*-bromocamphor that we have established constitutes a model procedure for the preparation of other enantiopure 7-*anti*-substituted norbornane-based chiral sources from other readily available enantiopure 3-*endo*-substituted camphors.

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References

1. For example; for **1a**, see: (a) Chu, Y.-Y.; Yu, C.-S.; Chen, C.-J.; Yang, K.-S.; Lain, J.-C.; Lin, C.-H.; Chen, K. *J. Org. Chem.* **1999**, *64*, 6993; for **2a**, see: (b) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729; (c) Yang, K.-S.; Lain, J.-C.; Lin, C.-H.; Chen, K. *Tetrahedron Lett.* **2000**, *41*, 1453; (d) Lin, C.-H.; Yang, K.-S.; Pan, J.-F.; Chen, K. *Tetrahedron Lett.* **2000**, *41*, 6815; (e) Chapuis, C.; Kucharska, A.; Jurczak, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4581; (f) Yang, K.-S.; Chen, K. *J. Org. Chem.* **2001**, *66*, 1676; for **3a**, see: (g) Ahn, K. H.; Lee, S.; Lim, A. *J. Org. Chem.* **1992**, *57*, 5065; (h) Ahn, K. H.; Lim, A.; Lee, S. *Tetrahedron: Asymmetry* **1993**, *4*, 2435.
2. Seo, R.; Ishizuka, T.; Abdel-Aziz, A. A.-M.; Kunieda, T. *Tetrahedron Lett.* **2001**, *42*, 6353.
3. For **5a**, see: (a) Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837; for **6a**, see: (b) Chang, C.-W.; Yang, C.-T.; Hwang, C.-D.; Uang, B.-J. *Chem. Commun.* **2002**, 54.
4. Schenone, P.; Tasca, A.; Bignardi, G.; Mosti, L. *Eur. J. Med. Chem.-Chim. Ther.* **1975**, *10*, 412.
5. For example, see: (a) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869; (b) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1737; (c) Suzuki, Y.; Ogata, Y.; Hiroi, K. *Tetrahedron: Asymmetry* **1999**, *10*, 1219; (d) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4127; (e) Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2000**, *41*, 4587; (f) 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.
6. On the preparation of acid **8b**, see: 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 and references cited therein.
7. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2001**, *12*, 189.
8. A dispersion of **11** in 35% HCl was stirred at 36°C for 3 days. After standard work up, pure (1*R*,7*S*)-7-bromo-3,3-dimethyl-2-oxonorbornane-1-carboxylic acid **8c** was obtained as a white solid (85% yield). $[\alpha]_D^{20}$ −58.6 (3.2, $CHCl_3$). Mp 145–146°C (decomposes). FTIR, ^1H and ^{13}C NMR, MS and HRMS agree with the structure.
9. A dispersion of **11** in 35% HCl was stirred at refluxing temperature for 48 h. After standard work up, a mixture of (1*R*,5*S*,8*R*)- and (1*R*,5*S*,8*S*)-4,4-dimethyl-2-oxa-3-oxobicyclo[3.3.0]octane-8-carboxylic acid **12** (*anti*/*syn* = 77/23) was obtained as a white solid (80% yield). FTIR, ^1H and ^{13}C NMR and MS agree with the structures. An analytical sample of the major *anti* epimer (1*R*,5*S*,8*R*) can be easily obtained from the mixture by crystallization

in $Et_2O/CHCl_3$. $[\alpha]_D^{20}$ −109 (0.7, MeOH). Mp 151–153°C. HRMS agree with the structure.

10. 2-Oxa-3-oxobicyclo[3.3.0]octanes are interesting intermediates in prostaglandin syntheses; for example, see: (a) Kabi Pharmacia AB, Sweed. *PCT Int. Appl.* 23pp; (b) Corey, E. J.; Amer, U. Y. *Acad. Sci.* **1971**, *180*, 24; (c) Kuthan, J.; Bohm, S.; Mostecky, J. *Collect. Czech. Chem. Commun* **1980**, *45*, 2179 and references cited therein; (d) Bindra, J. S. In: *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1981; Vol. 4, p. 353.
11. Related to this kind of bromine-assisted fragmentation in 7-*anti*-bromonorbornan-2-ones, see Ref. 7 and other references cited therein.