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Unusual Cyclopropanation of 9-Bromocamphor Derivatives: A Novel Formal C(1)–C(7) Bond Cleavage of Camphor

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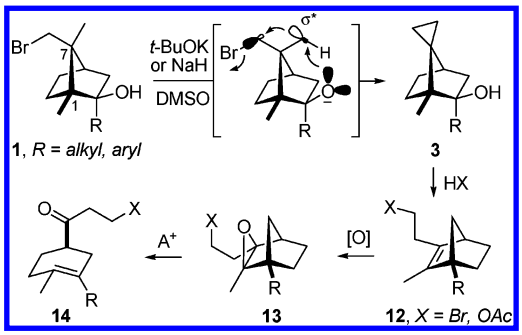
ABSTRACT



An unusual cyclopropanation of 9-bromocamphor derivatives 1 to a 7-spiro-cyclopropyl camphor derivative 3 was effected by the action of potassium *tert*-butoxide (or sodium hydride) in warm DMSO. The *exo*-hydroxy group and a non-hydrogen *endo*-substituent at C(2) have proven to be essential structural elements, and the solvent DMSO has proven to be the sole effective reaction medium. Tricyclic compound 3 undergoes a facile tandem Wagner–Meerwein rearrangement–cyclopropyl ring-opening under mild acidic conditions, leading to norbornenyl derivative 12 and subsequent Meinwald rearrangement of bicyclic epoxide 13 to a formal C(1)–C(7) bond cleavage product 14.

The uniqueness of the bicyclic structure of camphor is illustrated by a wide variety of intriguing structural transformations that frequently involve fascinating rearrangement processes.[1] Studies on these transformations have produced much chemical knowledge on theoretical and mechanistic aspects of organic chemistry in the past century and offered synthetically useful chiral building blocks from readily available natural camphor.[1] We report in this Letter an unusual cyclopropanation of C(2) *endo*-alkylated 9-bromocamphor derivative **1** to a tricyclic 7-spiro-cyclopropyl camphor **3** by the action of potassium *tert*-butoxide (or sodium hydride) in warm DMSO.

As shown in Scheme 1, upon treatment of a warmed (70 °C) DMSO solution of C(2) *endo*-alkylated 9-bromocamphor derivative **1**, prepared from 9-bromocamphor (**2**)[2] by an *endo*-selective carbonyl addition with an organocerium reagent,[3] with potassium *tert*-butoxide (*t*-BuOK) or sodium hydride (NaH) under a nitrogen atmosphere, a rapid and clean transformation took place as judged by TLC. A formal dehydrobrominative product was isolated in generally good to excellent yield and characterized spectroscopically and

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(1) For extensive reviews, see: (a) Money, T. *Nat. Prod. Rep.* **1985**, 253. (b) Money, T. In *Studies in Natural Products Chemistry*; Rahman, A. U., Ed.; Elsevier: New York, 1989; Vol. 4, pp 625−697.

(2) Prepared from natural *D*-camphor in three steps according to: Cachia, P.; Darby, N.; Eck, C. R.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 359.

(3) Dimitrov, V.; Brabantov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, *35*, 6713.

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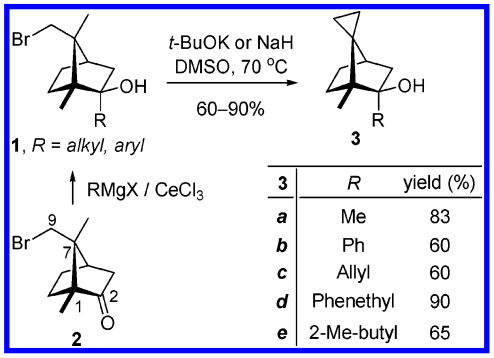
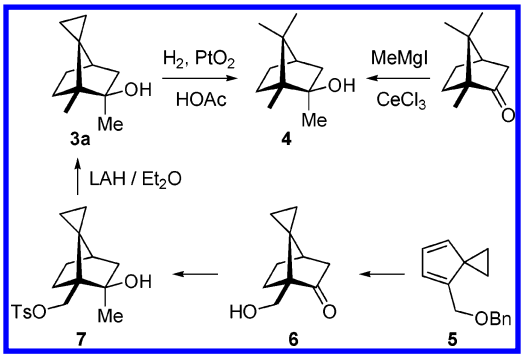
Scheme 1. Unusual Cyclopropanation of **1**



3	R	yield (%)
a	Me	83
b	Ph	60
c	Allyl	60
d	Phenethyl	90
e	2-Me-butyl	65

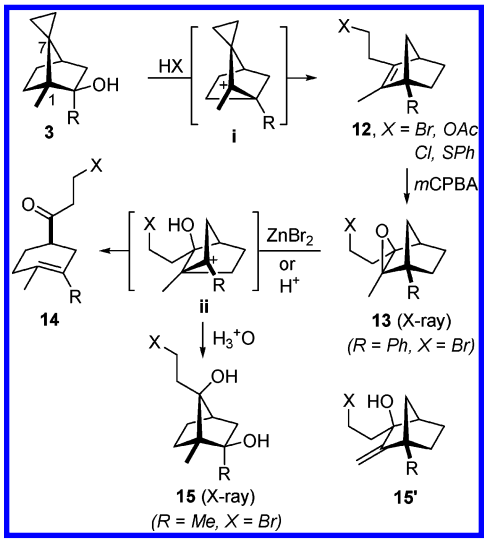
by further chemical transformations (Schemes 2 and 3) as an unusual 7-spiro-cyclopropyl camphor derivative **3**.[4] A small amount (<10%) of nucleophilic substitution product

Scheme 2 Alternative Synthesis and Hydrogenolysis of **3a**

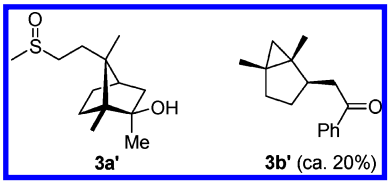


(i.e., **3a′**, as a mixture of diastereomers) by methylsulfinyl carbanion was also obtained.[5] In the case of **1b** (R = Ph), a bicyclic product **3b′** (ca. 20%) corresponding to an anionic

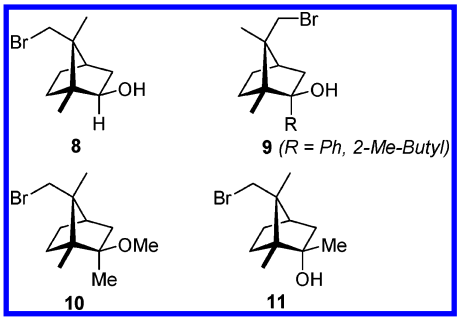
Scheme 3. Chemical Transformations of Tricyclic Alcohol **3**



C(1)−C(2) cleavage[6] and intramolecular cyclopropanation pathway was also detected along with the major spiro-cyclopropanation product **3b**.



The unusual tricyclic structure of 7-spiro-cyclopropyl camphor derivative **3a** was confirmed unequivocally by hydrogenolysis of the cyclopropane ring over Adams' catalyst in glacial acetic acid (Scheme 2), to a camphor derivative **4**, which is identical spectroscopically with an authentic sample[7] prepared from *D*-camphor by an *endo*-selective methylation. Furthermore, an alternative synthesis of **3a** was achieved[8] from spiro-cyclopropyl cyclopentadiene derivative **5** via Diels−Alder adduct **6**[9] and *endo*-methylated tosylate **7** as depicted in Scheme 2.



To further probe the structural requirements for this interesting γ-eliminative cyclopropanation reaction,[10] analogous compounds **8**−**11** derived from the corresponding bromocamphor derivatives were subjected to the same reaction conditions (Scheme 1). Intriguingly, *exo*-hydroxy derivative **8**,[11] an analogue of **1** with R = H, decomposed gradually at 80−100 °C. C(2)-Alkylated 8-bromocamphor derivative **9**[12] did not undergo similar cyclopropanation, and no dehydrobromination product could be detected even at refluxing temperature (180 °C). The methyl ether **10** and isomeric *endo*-hydroxyl derivative **11**[13] of **1a** have been proven experimentally to be inert substrates.

On the basis of the above facts, it appears that the free *exo*-hydroxy group and a non-hydrogen (carbogenic) *endo*-

(4) See Supporting Information for experimental details and data.

(5) A substantial amount (up to 40%) of this product was produced when a DMSO solution of the methylsulfinyl carbanion was preformed at 70−80 °C for 1 h prior to the addition of 9-bromocamphor alcohol **1**.

(6) For a relevant process involving a possible radical pathway, see: Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* **2003**, *5*, 2691.

(7) See Supporting Information for comparison.

(8) This synthetic work will be detailed elsewhere.

(9) For an alternative preparation, see: Föhlisch, B.; Bakr, D. A.; Fischer, P. *J. Org. Chem.* **2002**, *67*, 3682.

(10) Nickon, A.; Werstiuk, N. H. *J. Am. Chem. Soc.* **1967**, *89*, 3914, 3915, and 3917.

(11) Prepared from **2** by stereoselective reduction with $NaBH_4$ in ethanol or LAH in ether.[4]

(12) Prepared from the corresponding 8-bromocamphor similarly to *endo*-selective addition of organocerium reagent.[4]

substituent at C(2) are essential structural elements for effecting this unusual γ-eliminative cyclopropanation. Remarkably, the sole effective solvent[14] has proven to be anhydrous DMSO in combination with the use of strong bases (i.e., *t*-BuOK or NaH) capable of generating methylsulfinyl carbanion.[15] No cyclic ether or other dehydrobromination products were obtained from 9-bromocamphor derivatives **1** or **8** and 8-bromo derivative **9** by reaction with $Pb(OAc)_4$.[16] It is thus evident that this unusual cyclopropanation is anionic in character.[17]

The unusual cyclopropanation of **1** may be attributed to remarkable proximity and stereoelectronic effects in which the LUMO electron of the *exo*-alkoxy anion invades the σ^* orbital of the C−H bond of C(8)−CH_3 (intramolecular C_8-to-O proton transfer)[18] and subsequent intramolecular nucleophilic displacement of C(9)−Br (γ-eliminative cyclopropanation) as depicted in Figure 1 (cf. arrows in the brackets). The significance of the C(2) *endo*-alkyl substituent in **1**, exemplified by the intriguing reactivity difference of **1** vs **8**, may be a result of the delicate geometrical changes in this rigid bicyclic structure, which affects notably the ground and the corresponding transition state energetics.[19] Relevant examples are depicted in Figure 2 where subtle ring-structure variations render the intramolecular hydrogen abstraction of alkoxy radical intermediates, leading to a cyclic ether product (yield in parentheses) induced by the action of $Pb(OAc)_4$.[19,20]

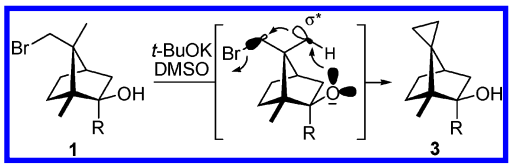


Figure 1. Orbital interaction diagram of cyclopropanation of **1**.

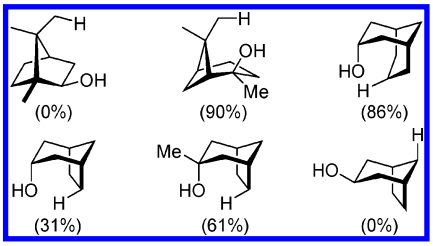


Figure 2. Intramolecular H-transfer of alkoxy radical.[19]

This unprecedented remote alkoxy anion-induced intramolecular cyclization may manifest the transition state arrangement of an enzymelike reaction in which unusual reactivity is achieved by directing reacting groups in close proximity.[21]

The determinative role of DMSO as the sole effective solvent may be attributed to its unique aprotic character[22] by generating a solvation-free alkoxy anion or participating in the intramolecular proton abstraction by forming a transient adduct with the alkoxy anion.[23] These mechanistic rationales will be further interpreted with the assistance of theoretical caculations[19] based on a force-field model (or DFT) in the future.

In view of the general interest in the chemistry of the nonclassical carbocations of camphor derivatives in recent history,[24] we found that the tricyclic spiro-cyclopropyl camphor derivative **3** underwent a facile tandem Wagner−Meerwein (WM) rearrangement−cyclopropyl ring-opening sequence under mild acidic conditions leading to the norbornenyl derivative **12** via a spiro-cyclopropyl cationic intermediate **i** generated from acid-mediated WM rearrangement of **3**. A variety of heteronucleophilic groupings (X) can be attached to the norbornenyl ring system as shown (Scheme 3). Stereoselective epoxidation with *m*-CPBA furnished the *exo*-epoxide **13** (mp 56−57 °C)[25] in good yield. Bicyclic epoxide **13** underwent Meinwald-type rearrangement[26] by the action of mild Lewis acid (i.e., $ZnBr_2$) or protic acid to give a cyclohexene derivative **14** smoothly, a formal C(1)−C(7) cleavage product of camphor skeleton,[1] via apparently an intermediary cationic intermediate **ii** that resulted from epoxy ring-opening-initiated WM rearrangement. Firm evidence for this pathway is provided by the production of bicyclic diol **15** (mp 135−136 °C) under the acidolysis conditions after a hydrolytic workup, whose structure was verified by a single-crystal X-ray diffraction analysis.[27] Norbornyl alcohol **15′** was also obtained along with **14** under various acidic conditions. The product **14** may

(13) Prepared selectively from 9-bromocamphor (**1**) via a C(2) spiro-epoxide by LAH reduction.[4]

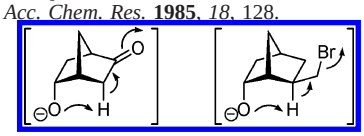
(14) Other solvents such as *t*-BuOH, THF, DMF, and HMPA were not effective.

(15) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866. (b) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128. (c) Arguello, J. E.; Penenory, A. B.; Rossi, R. A. *J. Org. Chem.* **1999**, *64*, 6115. Aqueous or weaker bases cannot effect this transformation.

(16) Partch, R. E. *J. Org. Chem.* **1963**, *28*, 276.

(17) It is not possible that a carbene species (via α-elimination) is involved in view of the inertness of compounds **8**−**11**.

(18) For examples involving through-space intramolecular H-transfer and theoretical accounts (below), see: (a) Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, *105*, 4996. (b) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128.



(19) Dorigo, A. E.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 1650 and references therein.

(20) Cf.: Hobbs, P. D.; Magnus, P. D. *J. Am. Chem. Soc.* **1976**, *98*, 4594.

(21) For research accounts on this topic, see: (a) Houk, K. N.; Tucker, J. A.; Dorigo, A. E. *Acc. Chem. Res.* **1990**, *23*, 107. (b) Menger, F. M. *Acc. Chem. Res.* **1993**, *26*, 206.

(22) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; Wiley-VCH: New York, 1988; pp 213−233.

(23) Cf.: Kwart, H.; Brechbiel, M. *J. Am. Chem. Soc.* **1981**, *103*, 4650.

(24) For reviews, see: (a) Olah, G. A.; Prakash, G. K. S.; Saunders, M. *Acc. Chem. Res.* **1983**, *16*, 440. (b) Olah, G. A. *J. Org. Chem.* **2005**, *70*, 2413.

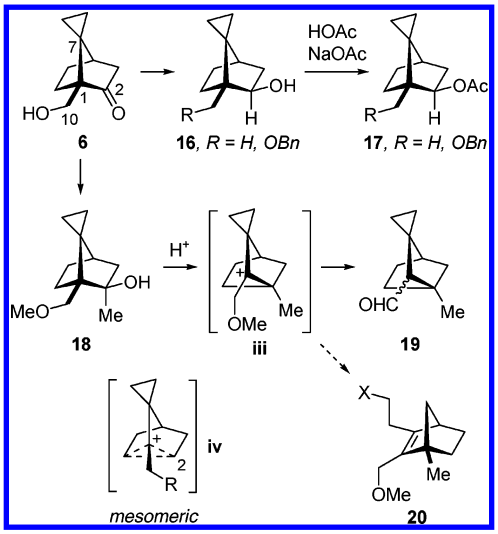
(25) X-ray crystallographic data of **13**: $C_{16}H_{19}BrO$, FW 307.22, orthorhombic, space group $P2_12_12_1$, a = 8.9507(8) Å, b = 25.614(2) Å, c = 30.160(3) Å, Z = 20, d_{calcd} = 1.476 g/cm^3, R_1 ($I > 2\sigma(I)$) = 0.0427, wR_2 (all data) = 0.0628. See Supporting Information for more details.

(26) (a) Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582. (b) Niwayama, S.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1994**, *116*, 3290.

be of synthetic value as a novel type of natural camphor-derived chiral synthon in organic synthesis[1] in which a heteroatomic group X and alkyl group R were incorporated.

Among the above transformations, the interesting tandem WM rearrangement−cyclopropyl ring-opening of **3** deserves further comment here. As shown in Scheme 4, *exo*-hydroxy

Scheme 4



camphor derivatives **16** derived from 10-hydroxy spiro-cyclopropyl camphor (**6**) were found to be inert toward the anticipated skeletal rearrangement under similar acidolysis conditions. Acetylation product **17** was obtained solely from the reaction mixture with the cyclopropane ring intact. Although the C(2)-*endo*-methylated derivative **18** underwent WM rearrangement with the promotion of acid, tricyclic aldehyde **19** (mixture of epimers) was the sole isolable product instead of the anticipated norbornenyl product **20**, apparently produced via a cationic species **iii** through a more favorable pinacol-type H-shift pathway due to the presence of a strong cation-stabilizing methoxy group.

The above facts may imply that formation of a highly symmetric nonclassical mesomeric cation species **iv** is favorable because of charge delocalization into the spiro-cyclopropyl ring system and is nonreactive toward nucleophilic attack. The incorporation of a carbogenic substituent at C(2) (i.e., Me) would destabilize this compact cationic structure and thus induce the subsequent nucleophilic reactions (cf. **18** → **19** and **3** → **12**). Interestingly, the carbogenic *endo*-substituent at C(2) is not only essential for the unusual γ-eliminative cyclopropanation of **1** but also determinative for the skeletal rearrangement of the spiro-cyclopropyl camphor derivative **3**, which is another example of the manifestation of the delicate relationship between chemical structure and reactivity in the unique camphor series.[1]

In summary, an unusual γ-eliminative cyclopropanation reaction of C(2)-alkylated camphor derivative **1** to **3** was discovered and rationalized using remarkable proximity and angular effects, which may be of value in understanding some relevant enzyme-catalyzed cyclopropanation reactions such as the presqualene synthesis.[28] Some intriguing skeletal transformations of spiro-cyclopropyl camphor derivatives **3** were investigated that add some new knowledge in the rich chemistry of camphor and relevant nonclassical cations. The formal cleavage of the C(1)−C(7) bond of camphor derivatives and a resulting novel type chiral synthon (i.e., **14**) may be useful in organic synthesis.

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Supporting Information Available: Experimental procedures, spectral data, and copies of spectra for compounds **1**, **3**, **4**, and **8**−**19** and CIF files for compounds **13** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051141E

(27) X-ray crystallographic data of **15**: $C_{11}H_{19}BrO_2$, FW 263.17, orthorhombic, space group $P2_12_12_1$, a = 7.2349(15) Å, b = 7.3055(15) Å, c = 44.210(9) Å, Z = 8, d_{calcd} = 1.496 g/cm^3, R_1 ($I > 2\sigma(I)$) = 0.0647, wR_2 (all data) = 0.1490. See Supporting Information for more details.

(28) For a review, see: Julia, M. Y. *Chem. Soc. Rev.* **1991**, *20*, 129.