The Stereochemical Requirement in the Fragmentation of 9-Bromocamphor Derivatives. A New Class of Chiral Pool Elements Containing Asymmetric Quaternary Carbon Centers

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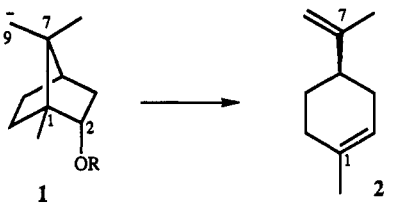
Summary: The fragmentation of 9-bromobornan-2-ol derivatives is dependent on both the orientation and identity of the leaving group at the 2-position. This has led to a synthesis of compounds containing useful quaternary carbon centers in carbocyclic six-membered rings, a previously unknown type of chiral pool elements.

We recently reported a mild fragmentation of camphor derivatives as a key transformation in four-step syntheses of furodysin and furodysinin, antiparasitic metabolites from sponges of the genus *Dysidea*.[1] We have also investigated other variants of this process to extend the synthetic utility of camphor and its derivatives as six-membered ring chiral pool elements.[2] We report preliminary results detailing both a stereochemical and a leaving group requirement in the fragmentation of 9-bromobornan-2-ol derivatives. Additionally, we have uncovered alternative fragmentations of camphor derivatives leading to carbocyclic six-membered ring chiral pool elements[3,4] containing useful quaternary carbon centers. In a recent compilation of 374 chiral pool elements[5] there were no examples of compounds containing chiral quaternary carbons except simple bicyclo[2.2.1] derivatives of camphor itself, camphoric acid, and fenchone.

The anionic fragmentation of the C1–C7 bond of camphor derivatives was made possible by the ready conversion of camphor to 9-bromocamphor via a well-known three-step process.[6] A slight variation of this experimental procedure can be carried out conveniently on multihundred-gram scales with an overall yield of 40%. Following our original reasoning,[1] if negative charge character could be developed at the C9 position in the presence of a leaving group at the C2 position, a fragmentation could occur cleaving the bridging C1–C7 bond (1 → 2). We predicted that an endo leaving group at C2 would participate in a fragmentation more readily than a C2-exo leaving group because of the more favorable overlap of the C2-endo bond with the C1–C7 bond. This is easily seen by inspection of Dreiding models and confirmed by molecular mechanics calculations[7] which show that the C7–C1–C2-exo dihedral



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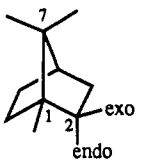

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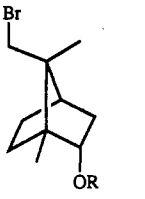
angle is approximately 91° while the C7–C1–C2-endo dihedral angle is approximately 165°, much closer to the optimum antiperiplanar arrangement of orbitals for fragmentation.[8] To address this question, several derivatives of alcohols **4** and **6** (R = H) were prepared.[1,9] To summarize our findings in this area, the fragmentation of substrates with exo leaving groups at C2 is not successful, leading only to the simple debromination products **7** in 75–90% yield. Fragmentation of the endo mesylate **4** (R = SO_2CH_3) leads to limonene (**2**) in 80% yield. Attempted fragmentation of substrates containing endo leaving groups at C2 *other than mesylate* also leads only to C9 debromination products (**5**), attesting to both a leaving group and a stereochemical requirement for C1–C7 bond fragmentation. This information suggested an alternative fragmentation of the camphor system which complements



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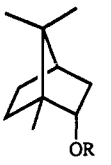

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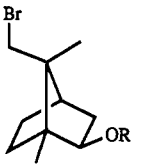
R = Ac
= $PO(OEt)_2$
= $COCF_3$
= SO_2CH_3



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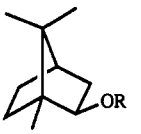

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(1) Richou, O.; Vaillancourt, V.; Faulkner, D. J.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 4729. Vaillancourt, V.; Agharahimi, M.; Sundram, U.; Richou, O.; Faulkner, D. J.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 378.

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(4) The use of limonene as a chiral pool substance has been attenuated by its inability to be functionalized cleanly in a stereo- and regiospecific fashion. This is especially true where the introduction of carbon-based substituents to the ring atoms is concerned. For a review of limonene chemistry, see: Thomas, A. F.; Bessiere, Y. *Nat. Prod. Rep.* **1989**, *6*, 291.

(5) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Ed.; Academic Press: New York, 1984; Vol. 4, pp 1–226. Notable omissions are the (+)- and (–)-Wieland–Miescher ketones and variants thereof, obtainable by the Hajos–Parrish asymmetric variant of the classical Robinson annulation. These important 11-carbon substances are analogous to camphor in many ways. They possess inherent steric and stereoelectronic biases which promote stereoselective formation of new C–C and C-heteroatom bonds at several positions on the skeleton, thus providing a variety of optically pure substances which are otherwise difficult to obtain.

(6) Lawrence, D. S. Ph.D. Dissertation, University of California Los Angeles, 1982.

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(8) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.

(9) All new compounds exhibit ^1H and ^{13}C NMR, IR, and high resolution mass spectra which are fully in accord with their structures. The purity of all new compounds was judged to be >95% by ^1H NMR. ^{13}C and ^1H NMR spectra of all new compounds are included in the supplementary material.

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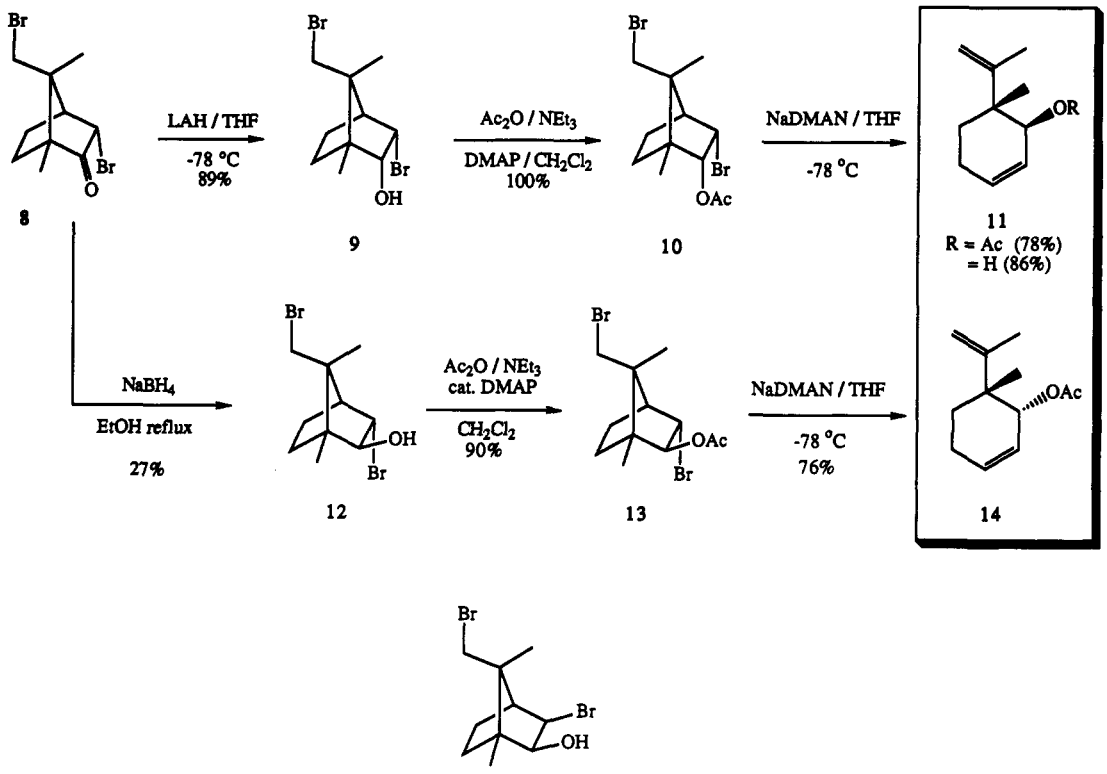
Scheme I



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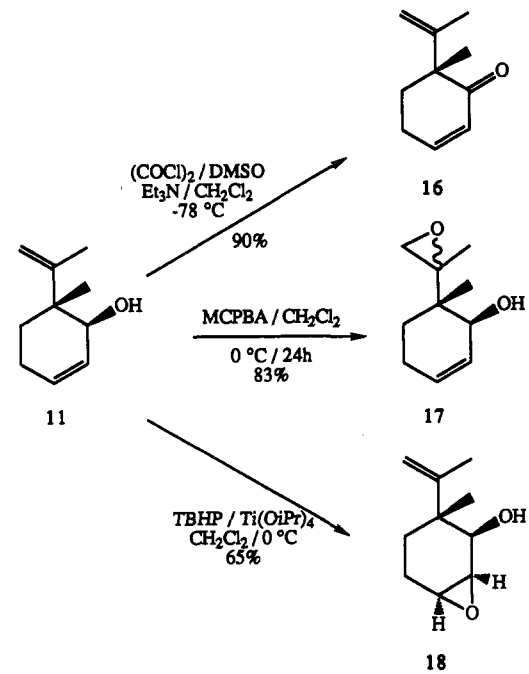
our previous work and leads to a second set of six-membered ring chiral pool elements.

endo-3,9-Dibromocamphor (**8**) is an intermediate in the synthesis of 9-bromocamphor, being produced by two successive brominations of optically pure camphor in about 50% overall yield. Although **8** is available commercially,[10] we routinely prepare it in 500-g quantities. Reduction of **8** with $LiAlH_4$ leads solely to the endo alcohol **9**, which could easily be converted to the acetate **10** (R = Ac). Treatment of **10** with sodium (dimethylamino)-naphthalenide (NaDMAN) at −78 °C leads to fragmentation of the C4–C7 bond with production of **11** (R = Ac) in 78% yield. No other products are observed in the ^1H NMR spectrum of the crude reaction product. Fragmentation of alcohol **9** itself also proceeded well, giving rise to allylic alcohol **11** (R = H) in 86% yield.

Treatment of **8** with $NaBH_4$ in refluxing EtOH provided the exo alcohol **12** in only 27% yield after chromatographic separation from the endo isomer **9** and **15**, an isomer resulting from epimerization at C3 and subsequent reduction. Meerwein–Verley–Ponndorf reduction of **8** resulted in a mixture of many compounds, of which the endo isomer **9** was the major product. Conversion of **12** to the acetate **13** (R = Ac) was straightforward. Fragmentation of this substance again proceeded well, producing the allylic acetate **14** in 76% yield. Thus, in four or five steps from camphor one may produce functionalized, optically pure six-membered ring chiral pool substances. Notably, the quaternary carbon possesses useful branching appendages in a methyl and an isopropenyl group, the latter providing a handle for further elaboration.

We briefly examined the manipulation of allylic alcohol **11**. Treatment of **11** under the Swern oxidation conditions outlined by Evans[11] gave **16** in 90% yield. In addition, we

Scheme II



studied the regioselective epoxidation of **11** using reagents specific for allylic alcohol systems. Reaction of **11** with MCPBA yielded, to our surprise, epoxide **17** exclusively as a 1:1 mixture of diastereomers in 83% yield. The regioisomeric epoxide **18** could be obtained in ca. 65% yield by treatment of **11** with catalytic amounts of $Ti(OiPr)_4$ and *tert*-butyl hydroperoxide (TBHP) at 0 °C. However, the reaction is not selective, since it also produces **17** in ca.

(10) This substance can be purchased from the Aldrich Chemical Co., Milwaukee, WI.

(11) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

20% yield. In any case, it is possible to differentiate the olefins which will facilitate further synthetic manipulations.

In summary, fragmentation studies have been carried out on various derivatives of 9-bromocamphor using aromatic radical anions as the electron transfer agent. The studies indicate that an endo orientation of a mesylate leaving group is crucial for fragmentation to occur. This has led to the development of C4-C7 fragmentation of readily available 3,9-dibromocamphor derivatives providing access to a class of six-membered ring chiral pool elements possessing a useful stereogenic quaternary carbon center.

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Supplementary Material Available: ^1H NMR and ^{13}C spectra of compounds 9-18 (22 pages). Ordering information is given on any current masthead page.

Articles

Synthesis of Proline-Valine Pseudodipeptide Enol Lactones, Serine Protease Inhibitors

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Pseudodipeptides of proline-valine that incorporate protio or halo enol lactone moieties have been synthesized from common acetylenic acid precursors; in each case, two diasteromers were prepared in enantiomerically pure form. The preparation began with isomeric propargylic alcohols derived from L-prolinal, which are further elaborated into the methyleneoxy valine pseudodipeptide analogues via an oxalactam intermediate. Stereochemical assignments were made by comparisons of nuclear Overhauser enhancement factors. The pseudodipeptide acetylenic acids could by cyclized to the protio enol lactones by mercuric salts and could be elaborated to tetrapeptide analogues either before or after cyclization. The relative stability of the two diastereomeric enol lactone systems toward intramolecular acyl transfer could be rationalized by molecular mechanics energy calculations on ground-state and tetrahedral intermediates believed to be involved in the reaction. While the halo enol lactones derived from the pseudotetrapeptides proved to be very unstable, they could be prepared from the *n*-butyl carbamate derivatives of the dipeptide. An evaluation of these protio and halo enol lactone systems as inhibitors of serine proteases will be discussed elsewhere.

The involvement of serine proteases in a variety of biological processes has stimulated the development of mechanism-based inhibitors for this class of enzymes.[1] Particular attention has been focused on the development of inhibitors of the serine protease human leukocyte elastase (HLE),[2a-c] because of its reputed involvement in serious degenerative diseases, such as emphysema.[3]

We have prepared various substituted 5- and 6-membered protio and halo enol lactones as serine protease inhibitors.[4a-e] We have found that some of the halo enol lactones are very potent inactivators ("suicide substrates") of α-chymotrypsin;[5a-c] these lactones react with the enzyme to give an acyl enzyme species possessing a reactive halomethyl ketone moiety which inactivates the enzyme by alkylating an active site nucleophile. Certain of the protio enol lactones, as well, act as alternate substrate inhibitors of α-chymotrypsin by forming extremely stable acyl enzyme intermediates.[4e,6]

In order to increase the specificity of these lactones toward their targeted serine proteases, we have prepared amino acid analogues which incorporate an enol lactone.[4c,d] We now report the synthesis of the enantiomerically pure enol lactone pseudodipeptides **1a,b** and **2a,b**. These compounds were prepared as potential inhibitors of human leukocyte elastase and were intended to mimic the dipeptide Pro-Val that terminates many oligopeptide substrates of HLE such as methoxysuccinyl-L-Ala-L-Ala-L-Pro-L-Val *p*-nitroanilide.[7]

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