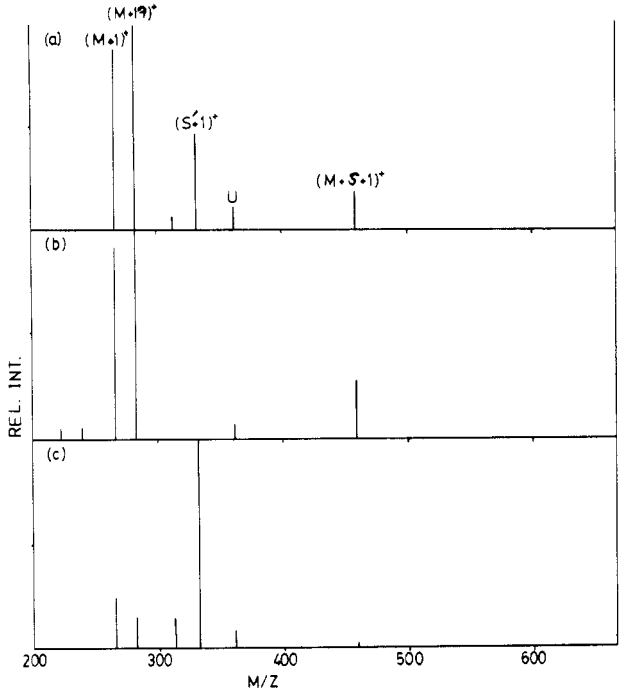

Figure 1. CIMS (CH_4) of a mixture of freeze-dried coffee, 18-crown-6, and 11α-hydroxyprogesterone: (a), (b), and (c) are three successive scans as the temperature of the ion source was raised from ~170 to 190 °C; the molecular weight of caffeine = S = 194, 18-crown-6 = M = 264; 11α-hydroxyprogesterone = S' = 330. An unidentified peak is marked U. Note the absence of the adduct ion at m/z 595 corresponding to the sterol.

hydrogen bonding between the amino nitrogen and the ether oxygens. The more intense adduct ions from amines compared to alcohols may perhaps be ascribed to the larger number of available hydrogens in the former for complexation with crown ether oxygens. In any case, this difference in binding—whatever be the underlying reason—could be of practical value for selective analysis of amino compounds in the presence of alcohols, ketones, esters, etc.

As an illustration of the selectivity achieved by using crown ethers, we cite an experiment in which commercial freeze-dried coffee mixed with a sterol was the analyte and 18-crown-6 was the reagent; at m/z >200 an adduct ion for caffeine was observed at m/z 459 but no adduct ion for the sterol or other compounds was displayed except possibly for one unidentified peak (see Figure 1).

It is significant that biologically important purines and pyrimidines such as adenine and cytidine produce intense adduct ions. We plan to explore the possibility of using crown ethers for easy detection of unusual bases from nucleic acids. The analysis of amino acids, dipeptides, and other amino acid derivatives by forming crown ether adducts is also under study.

Acknowledgment. We are grateful to Stevens Institute of Technology and the Office of Naval Research (N00014-83-C-0233) for the support of this research and the Schering–Plough Foundation for a generous grant for the chemical ionization mass spectrometry facility. We thank Provost R. Cotellessa, Dr. F. T. Jones, and A. Attridge for their interest and support.

Registry No. 1, 127-08-2; 2, 7681-82-5; 3, 56-41-7; 4, 60-35-5; 5, 142-96-1; 6, 495-69-2; 7, 62-23-7; 8, 56-40-6; 9, 70-47-3; 10, 74-79-3; 11, 968-21-8; 12, 13734-41-3; 13, 108-91-8; 14, 2470-68-0; 15, 71-36-3; 16, 13074-39-0; 17, 58-08-2; 18-crown-6, 17455-13-9; 12-crown-4, 294-93-9; methane, 74-82-8.

(8) Visiting Scholar from Zhejiang University supported by the People's Republic of China and Stevens Institute of Technology.
(9) Present addess: Mount Sinai School of Medicine, Department of Psychiatry, New York, NY, 10029.

Ajay K. Bose,* Om Prakash
Geng Yuan Hu,[8] James Edasery[9]
Department of Chemistry and Chemical Engineering
Stevens Institute of Technology
Hoboken, New Jersey 07030
Received December 22, 1982

A New Entry to Highly Functionalized Perhydroindans via Free Radical Cyclizations

Summary: Reductive alkylation of substituted benzoic acids followed by iodolactonization and free radical cyclization provides an efficient stereoselective route to *trans*-perhydroindans.

Sir: Free radical carbon–carbon bond-forming addition reactions are attracting renewed attention from synthetic organic chemists.[1-3] We have recently examined a route to fused carbocycles in which a radical cyclization plays a crucial role.[4] This report described the initial results of this study and in particular documents a promising new entry to highly functionalized perhydroindans.

We began our studies by examining the reaction sequence outlined in Scheme I. Birch reduction of *m*-toluic acid (1) followed by alkylation of the resulting dianion with 4-bromo-1-butene afforded acid **2** (91%),[5] which was converted to iodo lactone **3** ($NaHCO_3$–H_2O–Et_2O) in a 61% yield.[6,7] Treatment of **3** with tri-*n*-butyltin hydride and AIBN in benzene under reflux gave a separable mixture of isomeric lactones **5**, **6**, **7**, and **8** (87%; 1:12:2:6) presumably via cyclization of radical **4**.[8] The structures of **5**, **7**,[9]

(1) For notable early studies, see: Julia, M. *Rec. Chem. Prog.* **1964**, *25*, 3. Julia, M. *Pure Appl. Chem.* **1967**, *15*, 167. Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386. Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553.
(2) For recent carbocycle syntheses via intramolecular radical cyclizations, see: Bakuzis, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261. Buchi, G.; Wüest, H. *Ibid.* **1979**, *44*, 546. Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. Danishefsky, S.; Chackalamannil, S.; Uang, B.-J. *J. Org. Chem.* **1982**, *47*, 2231.
(3) For recent advances in intermolecular radical-mediated carbon–carbon bond formation, see: Giese, B.; Heuck, K. *Chem. Ber.* **1979**, *112*, 3759. Giese, B.; Zwick, W. *Ibid.* **1979**, *112*, 3766. Giese, B.; Meister, J. *Ibid.* **1977**, *110*, 2588. Giese, B.; Horler, H.; Zwick, W. *Tetrahedron Lett.* **1982**, *23*, 931. Kozikowski, A. P.; Nieduzak, T. R.; Skripko, J. *Organometallics* **1982**, *1*, 657. Burke, S. D.; Fobare, W. F.; Armistead, D. M. *J. Org. Chem.* **1982**, *47*, 3348. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.
(4) For relevant reviews, see: Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073 and references cited therein.
(5) Van Bekkum, H.; Van Den Bosch, C. B.; Van Minnenpathius, G.; De Mos, J. C.; Van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137.
(6) For a review, see: Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev. (Engl. Transl.)* **1971**, *40*, 272.
(7) For halolactonization of 1,4-dihydrobenzoic acids, see: Barnett, W. E.; Needham, L. L. *J. Org. Chem.* **1975**, *40*, 2843. Holbert, G. W.; Weiss, L. B.; Ganem, B. *Tetrahedron Lett.* **1976**, 4435. Bromolactonization of **2** afforded a mixture of β-and γ-lactones.
(8) Pure samples of **5**–**8** were obtained by GLC. From a preparative standpoint, lactone **6** (mp 106–107 °C) was crystallized directly from the product mixture in a 39% yield.
(9) The stereochemical details of **7** and the minor perhydroindans obtained in the cyclizations of **12**, **17**, and **23** are unknown. We suspect, however, that they are merely the C(7) isomers of the major perhydroindans.

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Scheme I

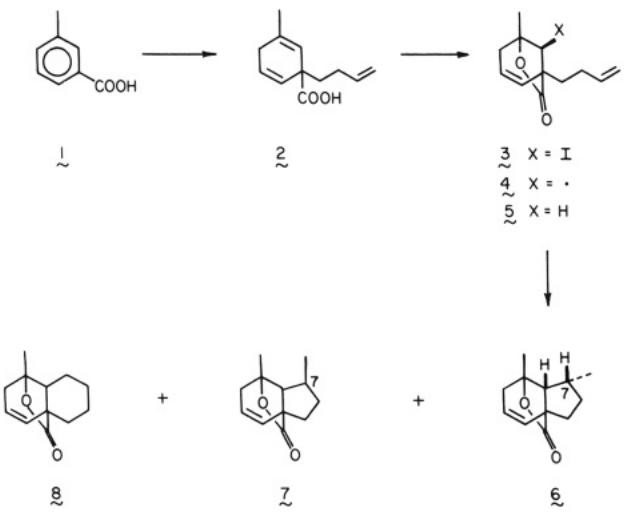
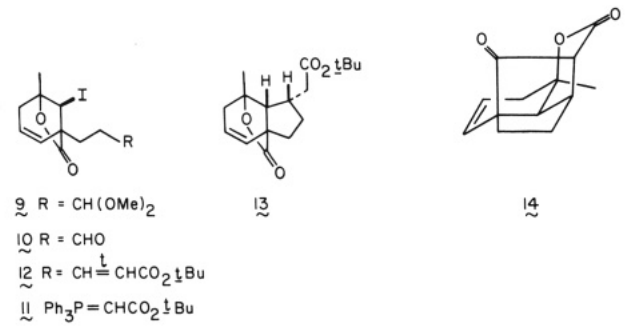


Chart I



and **8** were assigned on the basis of spectral data while the structure of **6** was established by X-ray crystallography.[10]

Several aspects of the free radical cyclization are notable. Radical **4** gives a 2:1 ratio of exo:endo cyclization products, contrary to the much larger exo:endo ratios observed for simple 5-hexenyl radicals.[4] The reason for this unusual partioning is uncertain at this time. In addition, both the endo and exo cyclizations proceed with high stereoselectivity. In the exo cyclization (**4** → **6**), we imagine that the formation of *trans*-perhydroindan **6** is in part due to the preference of the oxabicyclo[3.3.0]octane substructure for a cis ring fusion. The observed stereoselectivity at C(7) is consistant with results obtained in simpler carbocyclic systems.[11] The endo cyclization (**4** → **8**) affords a single perhydronaphthalene whose stereochemistry at C(6) remains unknown.[12]

Although radical **4** cyclizes to a mixture of products, reports from these[13] and other[14] laboratories suggest that by controlling olefinic substitution patterns, it should be possible to guide the anellation sequence toward perhydroindan or perhydronaphthalene formation. This point is illustrated in part by the reaction sequence outlined in Chart I. Thus, reductive alkylation[5] of **1** with with 3,3-dimethoxy-1-bromopropane[15] followed by lactonization of the resulting dihydrobenzoic acid gave iodo lactone **9** (74%). Hydrolysis of the acetal followed by treatment of the resulting aldehyde **10** (90%; mp 88–89 °C) with phosphorane **11**[16] gave iodo ester **12** (mp 110–111 °C) in a 93% yield. Reductive cyclization of **12** (*n*-Bu_3SnH–AIBN–PhH) gave a 6:1 mixture of isomeric perhydroindans (96%) from which **13** (mp 104–105 °C) could be crystallized in a 73% yield.[9,17] Chemical evidence for the stereochemical assignment of **13** was obtained as follows. Treatment of **13** with lithium hexamethyldisilazide in ether followed by treatment of the resulting mixture of β-keto esters with trifluoroacetic acid gave keto lactone **14** (82%, mp 124–125 °C). No stereoisomers of **13** are capable of undergoing the observed Dieckman condensation.

We also explored the use of other benzoic acid derivatives in this reaction sequence.[18] Two examples are outlined in Chart II. Iodo lactone **15** was prepared in a straightforward manner from *m*-anisic acid and 4-bromo-1-butene (66%). Johnson–Lemieux cleavage of the terminal olefin[19] gave aldehyde **16**, which was directly converted to iodo ester **17** (57%) upon treatment with carbethoxymethylidenetriphenylphosphorane. Reductive cyclization of **17** afforded a 4:1 mixture of two diastereomeric perhydroindans (81%) in which we suspect **18** is the major steroisomer.[9,17] Finally, reductive alkylation of benzoic acid with 2-(2-bromoethyl)-1,3-dioxolane[20] gave acid **19** (94%). Attempts to efficiently convert **19** to iodo lactone **21** met with failure. Treatment of **19** with diphenylphosphoryl azide[21] and pyrrolidine, however, gave amide **20** (85%; mp 79–80 °C), which was converted to **21** (75%; mp 116–117 °C) upon treatment with iodine in aqueous tetrahydrofuran. Ketal hydrolysis (H_2O–HCOOH, 1:4; 90%) gave aldehyde **22** (mp 77–78 °C), which afforded iodo ester **23** (90%) upon treatment with phosphorane **11**. Reductive

(10) We thank Dr. Judith Gallucci for performing the crystal structure of **6** at The Ohio State Chemistry Department Crystallography Facility. Lactone **6** crystallizes in space group $P2_1/c$ with $Z = 4$ in a cell of dimensions $a = 8.966$ (1) Å, $b = 8.507$ (1) Å, $c = 13.502$ (1) Å, and $\beta = 94.45$ (1)° at 20 °C. Full-matrix least-squares refinement on the set of 1801 unique reflections with $F_o^2 > 26(F_o^2)$ yielded an R (on F) of 0.045 for the 191 variables (non-hydrogen atoms treated anisotropically and hydrogen atoms treated isotropically).

6

(11) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811. Agosta, W. C.; Wolff, S. *J. Chem. Res. (S)* **1981**, 78.

(12) A recent study suggests that **8** may have a trans C(1)–C(6) fusion: Coblens, K. E.; Muralidharan, V. B.; Ganem, B. *J. Org. Chem.* **1982**, *47*, 5041.

(13) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430.

(14) Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737.

(15) Battersby, A. R.; Buckley, D. G.; Staunton, J.; Williams, P. J. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2550.

(16) Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M. *Tetrahedron* **1976** *32*, 275.

(17) The ratio of stereoisomers was determined by integration of appropriate signals in the 200-MHz ^1H NMR spectrum of the purified mixture.

(18) For other anellation sequences that rely on reductive alkylation of benzoic acids, see: Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1977**, *42*, 1794. Tamai, Y.; Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1982**, *502*. Mander, L. N.; Hamilton, R. J. *Tetrahedron Lett.* **1981**, *22*, 4115.

(19) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478. Evans, D. A.; Sims, C. L. *Tetrahedron Lett.* **1973**, 4691.

(20) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.

(21) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

Chart II

15 R = CH=CH$_2$
16 R = CHO
17 R = CH=CHCO$_2$Et

18 X = OMe, R = Et
24 X = H, R = tBu

19 X = OH, R = CH(OCH$_2$CH$_2$O)
20 X = N⟨⟩, R = CH(OCH$_2$CH$_2$O)

21 R = CH(OCH$_2$CH$_2$O)
22 R = CHO
23 R = CH=CHCO$_2$tBu

cyclization of **23** gave a 7:1 mixture of diasteromeric perhydroindans (93%) with **24** as the major stereoisomer.[9,17,22]

In summary, reductive alkylation of benzoic acid derivatives followed by iodolactonization and free radical cyclization affords an efficient new route to perhydroindans. The radical cyclizations proceed with modest to excellent steroselectivity, a major concern with using free radical carbon–carbon bond-forming reactions in the synthesis of complex molecules. Applications of this protocol to synthesis of carbocyclic natural products as well as studies directed toward understanding features that govern exo–endo partitioning of radicals of type **4** are currently being addressed.[23]

Acknowledgment. We thank the National Science Foundation for generous support of this work. We also thank the National Institutes of Health for a grant (GM-27431) used to purchase high-field NMR instrumentation.

Registry No. **1**, 99-04-7; **2**, 85585-43-9; **3**, 85585-44-0; **5**, 85585-45-1; **6**, 85585-46-2; **7**, 85647-17-2; **8**, 85585-47-3; **9**, 85585-48-4; **10**, 85585-49-5; **11**, 35000-38-5; **12**, 85585-50-8; **13**, 85585-51-9; 7β-**13**, 85612-02-8; **14**, 85585-52-0; **15**, 85585-53-1; **16**, 85585-54-2; **17**, 85585-55-3; **18**, 85585-56-4; 7β-**18**, 85647-18-3; **19**, 85585-57-5; **20**, 85585-58-6; **21**, 85585-59-7; **22**, 85585-60-0; **23**, 85585-61-1; **24**, 85585-62-2; 7β-**24**, 85647-19-4; 4-bromo-1-butene, 5162-44-7; 1-bromo-3,3-dimethoxypropane, 36255-44-4; 1-(3,3-dimethoxypropyl)-3-methylcyclohexa-2,5-dienoic acid, 85585-63-3; *m*-anisic acid, 586-38-9; benzoic acid, 65-85-0; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4.

Supplementary Material Available: Procedures for the preparation of **9**, **10**, **12**, and **13** (3 pages). Ordering information is given on any current masthead page.

(22) Lactone **24** was converted to demethyl-**14** (72%; mp 111–112 °C) via the same reaction sequence used to convert **13** to **14**.

(23) Preliminary experiments have shown that the radicals derived from **15** and *rel*-(1*S*,5*S*,8*S*)-1-(3-buten-1-yl)-8-iodo-6-oxabicyclo[3.2.1]-oct-2-en-7-one display endo–exo partitioning similar to that observed for **4**.

Che-Ping Chuang, David J. Hart*

Department of Chemistry
The Ohio State University
Columbus, Ohio 43210

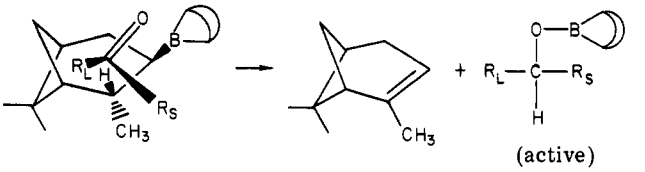
Received March 1, 1983

Asymmetric Reduction of Prochiral α-Halo Ketones with *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane

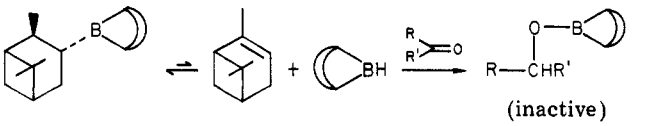
Summary: *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane reduces aryl α-haloalkyl ketones to the corresponding halohydrins in nearly quantitative chemical yield and high optical induction. This reagent yields somewhat lower optical induction in the case of the aliphatic analogue, 1-bromo-3-methyl-2-butanone. The halohydrins can be converted to the corresponding chiral epoxides or dehalogenated to the parent alcohol with retention of optical activity.

Sir: In the last couple of years, *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (**1**, Midland's reagent) has emerged as an exceptionally valuable reagent for the asymmetric reduction of various carbonyl compounds.[1-3] The reagent embodies attractive features such as ready availability[4] in both *d* and *l* forms, a mild and simple experimental procedure, and enzyme-like selectivity in many instances. Whereas the reduction proceeds rapidly with aldehydes and acetylenic ketones, the reaction time is often inconveniently long for other cases such as simple ketones. We discovered that the use of neat reagents or concentrated solutions overcomes this difficulty in many cases, making the Midland procedure more general.[3]

Midland and co-workers have shown that electron-withdrawing substituents on the carbonyl compound increase the rate of reduction.[1,5] We have also observed that ester[3,6] or cyano[7] groups attached directly to the carbonyl function bring about a major increase in the rate of reduction. Although not necessarily true in all cases, usually an enhanced reduction rate also increases the optical induction since it favors the cyclic mechanism (eq 1) over



(active) (1)



(inactive) (2)

the dissociation mechanism (eq 2). We reasoned that an electron-withdrawing substituent such as halogen substituted α to the carbonyl group should also provide a similar rate increase and improved asymmetric induction. Moreover, the reduction products in this case would be halohydrins, readily converted to the valuable optically active epoxides or to the parent optically active alcohols.

Our expectation was realized in the reduction of α-bromoacetophenone (**2**). The reduction, using 100% excess

(1) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.
(2) Midland, M. M.; McDowell, D. D.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.
(3) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606.
(4) Now commercially available from Aldrich Chemical Co. under the name Alpine-borane.
(5) Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525.
(6) Midland and co-workers have observed similar effect in the reduction of methyl benzoylformate. Private communication from Dr. Midland.
(7) Unpublished results. Experiment in progress.

0022-3263/83/1948-1784$01.50/0