mixture of 40% sodium bisulfite and ethanol (4/1 v/v).[13] The organic phase was dried and concentrated and the residue distilled, affording 2.63 g (65%) of phthalan **6a** as a colorless oil: bp 78–80 °C (0.25–0.30 torr); ^{1}H NMR ($CDCl_3$) δ 1.20–2.70 (m, 13, CH_3, cyclohexyl CH_2's), 5.36 (q, J = 7 Hz, 1, benzylic methine), 7.10–7.50 (m, 4, Ar H).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.85; H, 8.88.

***o*-Bromo-α,α-dimethylbenzyl Chloride (3b).** *o*-Bromo-α,α-dimethylbenzyl alcohol[15] (11.0 g, 51 mmol) was protected from moisture, cooled to 0 °C, and magnetically stirred while dry hydrogen chloride was bubbled through it for 5.5 h. The mixture was poured into ice–water and the organic layer taken up in ether. The ether solution was washed with saturated sodium bicarbonate solution, dried, and concentrated. Distillation of the residue afforded 8.0 g (67%) of **3b** as a colorless oil: bp 58–62 °C (0.02 torr);[16] ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 6, CH_3), 7.04–7.75 (m, 4, Ar H).

Anal. Calcd for $C_9H_{10}BrCl$: C, 46.29; H, 4.32; halogen, 30.36 (as Cl). Found: C, 46.65; H, 4.33; halogen, 30.51 (as Cl).

Bromine–Lithium Exchange of *o*-Bromo-α,α-dimethylbenzyl Chloride (3b). (a) Conversion to α,α-Dimethylbenzyl Chloride (5b). Following the usual precautions,[3] we treated 4.67 g (20 mmol) of **3b** in 130 mL of tetrahydrofuran and 30 mL of hexane at −100 °C with 20 mmol of butyllithium and maintained the mixture at the same temperature for 1 h. The resulting yellow slurry was poured into cold 5% hydrochloric acid and the organic material extracted with ether (3 × 100 mL). The ether solution was dried and concentrated to afford 3.47 g of oil which, upon examination by ^{1}H NMR, appeared to be 73% **5b** (comparison with an authentic sample[17]). Vacuum distillation of the oil was accompanied by severe decomposition but yielded 0.46 g of **5b**: bp 49–54 °C (2.2–2.8 torr) [lit.[16] bp 65–68.5 °C (6.5–7.0 torr)]; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 6, CH_3), 7.20–7.70 (m, 5, Ar H).

(b) Conversion to 3′,3′-Dimethylspiro[cyclohexane-1,1′-phthalan] (6b). The organolithium reagent (**4b**) was prepared from 4.67 g (20 mmol) of **3b** at −100 °C, was treated with 2.94 g (30 mmol) of cyclohexanone as in the preparation of the lower homologue (**6a**), and was worked up in the same way, except that before the final distillation the crude product was refluxed for 1 h in 20% alcoholic potassium hydroxide solution. This mixture was diluted with 150 mL of water and extracted with ether. The ether extract was dried and concentrated, and the residue was distilled to afford 1.06 g (25%) of **6b**: bp 87–90 °C (1.0–0.9 torr) [lit.[15] bp 56–58 °C (0.08 torr)];[18] ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 6, CH_3), 1.72 (br s, 10, cyclohexyl CH_2's), 6.98–7.30 (m, 4, Ar H).

(c) Conversion to 3,3-Dimethyl-*N*-phenylphthalimidine (7). The organolithium reagent (**4b**) was prepared from 4.67 g (20 mmol) of **3b**, and a solution of phenyl isocyanate (2.62 g, 22 mmol) in 25 mL of hexane was added over a period of 5 min. The reaction mixture which rapidly lost its cloudy appearance was stirred at −100 °C for 15 min and then warmed to 25 °C over 1.5 h. The reaction mixture was poured into water and the product taken up in ether.

The ethereal solution was dried and concentrated, and the semisolid residue was crystallized from chloroform–ligroin as yellow crystals: 1.64 g (35%); mp 186–190 °C. One recrystallization afforded 1.36 g (29%) of faintly yellow crystals of **7**: mp 191–192.5 °C (lit.[19] mp 189–190 °C); ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 6, CH_3), 7.20–8.02 (m, 9, Ar H); IR ($CHCl_3$) 1680 cm^{-1} (C=O).

4-(*o*-Bromophenyl)-2-butanol. To a stirred solution of 21.12 g (93 mmol) of 4-(*o*-bromophenyl)-2-butanone[10] in 200 mL of 2-propanol was added a suspension of sodium borohydride (1.90 g, 50 mmol) in 50 mL of 2-propanol, and the mixture was refluxed for 24 h with stirring. After the solution cooled, 45 mL of water and then 13 mL of acetic acid were added. The mixture was concentrated under reduced pressure and the residue partitioned between water and ether. The ether solution was dried and concentrated. Distillation of the residue through a 10-cm column gave a low-boiling forerun followed by 9.28 g (43.5%) of a colorless oil: bp 87.5–89 °C (0.10 torr); ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6 Hz, 3, Me), 1.78 (m, 2, CH_2CHOH), 2.22 (bs, 1, OH, exchangeable), 2.86 (m, 2, CH_2AR), 3.86 (m, 1, CHOH), 6.90–7.64 (m, 4, Ar H); IR (neat), 3350 cm^{-1} (OH).

Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72; Br, 34.88. Found: C, 52.59; H, 5.98; Br, 35.16.

4-(*o*-Bromophenyl)-2-bromobutane (8b). A solution of 13.75 g (60 mmol) of 4-(*o*-bromophenyl)-2-butanol in 50 mL of ether was cooled in an ice bath and stirred while 16.3 g (60 mmol) of phosphorus tribromide was added over a period of 15 min. The ice bath was removed and stirring continued for 21 h. The reaction mixture was poured into a mixture of 200 g ice and 100 mL of saturated sodium bicarbonate solution. When the ice melted, the phases were separated, and the aqueous phase was extracted with ether. The combined organic phases were dried and concentrated. Distillation of the residue through a 10-cm column gave a fraction as a colorless oil: 7.5 g (43%); bp 86–88 °C (0.07–0.08 torr);[20] ^{1}H NMR ($CDCl_3$) δ 1.70 (d, J = 6 Hz, 3, CH_3), 2.10 (m, 2, CH_2CHBr), 2.90 (m, 2, CH_2Ar), 4.10 (m, 1, CHBr), 6.90–7.60 (m, 4, Ar H).

Anal. Calcd for $C_{10}H_{12}Br_2$: C, 41.13; H, 4.14; Br, 54.73. Found: C, 41.16; H, 4.26; Br, 54.91.

Bromine–Lithium Exchange of 8b. 1-Methylindan (10b). A solution of 4.38 g (15 mmol) of **8b** in 100 mL of tetrahydrofuran and 25 mL of hexane was cooled to −100 °C and 17 mmol of butyllithium added at such a rate that the temperature did not exceed −97 °C. The progress of the exchange and cyclization reaction was monitored by ^{1}H NMR analysis of quenched samples. Exchange was complete after only 15 min, but no cyclization was observed after a total of 30 min at −100 °C. The temperature was next allowed to rise to −78 °C and remain there for 1 h. The evidence was that very little cyclization had occurred. The temperature was allowed to rise to 25 °C (45 min) and remain there for 3 h. The mixture was poured into water, the organic layer separated, and the water extracted with ether. The combined organic phases were dried and concentrated. The residue was distilled, yielding 0.75 g (38%)[12] of colorless oil: bp 61–62 °C (5.7 torr) (lit.[21] bp 183–185 °C); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6 Hz, 3, CH_3), 1.60–2.30 (m, 2, CH_2 at C-2), 2.84 (m, 2, $ArCH_2$), 3.16 (m, 1, CH), 7.16 (s, 4, ArH).

Registry No. 3a, 57739-76-1; **3b**, 7073-71-4; **4a**, 79044-15-8; **4b**, 79044-16-9; **5a**, 672-65-1; **5b**, 934-53-2; **6a**, 79044-17-0; **6b**, 59043-55-9; **7**, 53890-83-8; **8b**, 79044-18-1; **10b**, 767-58-8; cyclohexanone, 108-94-1; *o*-bromo-α,α-dimethylbenzyl alcohol, 7073-69-0; phenyl isocyanate, 103-71-9; 4-(*o*-bromophenyl)-2-butanol, 67130-96-5; 4-(*o*-bromophenyl)-2-butanone, 3506-68-1.

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Regioselective Oxidations of Primary Alcohols in 1,4-Diols

Michael P. Doyle* and Vahid Bagheri

Department of Chemistry, Hope College, Holland, Michigan 49423

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Numerous oxidative methods are currently available for the selective oxidation of secondary alcohols in primary, secondary diols.[1-5] However, since electronic stabilization

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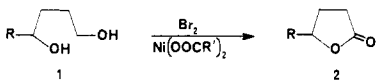
Table I. Oxidations of 1,4-Diols by Bromine in the Presence of Nickel(II) Alkanoates

R	$Ni(OOCR')_2$	% yield (2)[a]
C_6H_5	2-ethylhexanoate	58
	benzoate	32
n-C_4H_9	2-ethylhexanoate	70
	benzoate	36
n-C_6H_{13}	2-ethylhexanoate	68
	benzoate	35

[a] Yields reported are for isolated products. Reactions were performed in anhydrous acetonitrile at 25 °C, using 5.0 molar equiv of the nickel(II) alkanoate.

resulting from hydrogen abstraction favors oxidation at the secondary position, selective oxidation of primary alcohols in primary,secondary diols continues to represent a notable synthetic challenge. The use of silver(I) carbonate–Celite is currently a preferred method for these transformations[6-8] even though substantial excesses of this expensive oxidant must be employed to achieve moderate yields of the desired products. Platinum-catalyzed autoxidations have also been employed[8-10] but are capricious. Recently, the effectiveness of $RuCl_2(PPh_3)_3$ in benzene as a stoichiometric reagent for selective oxidations of primary alcohols has been described.[11]

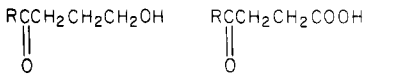
We have reported the use of benzoyl peroxide in combination with nickel(II) bromide for the highly selective oxidation of 2,2-disubstituted-1,4-butanediols to their corresponding β,β-disubstituted-γ-butyrolactones.[12] More recently, molecular bromine in combination with nickel(II) benzoate has been advanced as the superior procedure for these transformations.[13] We now report the use of bromine with nickel(II) 2-ethylhexanoate for the selective contrathermodynamic oxidation of primary,secondary 1,4-diols to lactones (eq 1).



1 2 (1)

Treatment of diol 1 with 5.0 molar equiv of the nickel(II) alkanoate in anhydrous acetonitrile followed by dropwise addition of molecular bromine in acetonitrile results in the disappearance of the bromine color and the resulting formation of lactone 2. Optimal yields of this product were obtained when bromine was employed in 1.8 molar excess relative to the nickel(II) alkanoate, and reactions were allowed to proceed for 6 h at 25 °C. Results with representative diols and nickel(II) alkanoates are presented in Table I.

The unique capabilities of nickel(II) alkanoates to direct the course of bromine oxidation is indicated by results from comparable processes. Oxidation of 1 by bromine generated through the action of lithium bromide on benzoyl peroxide in acetonitrile produced keto alcohol 3 in variable



3 4

yields (R = C_6H_5, 60%; R = C_6H_{13}, 32%), but no lactone was observed. Similar results were obtained from bromine oxidations in methylene chloride–hexamethylphosphoramide.[3] Keto acid 4, presumed to result from the oxidation of 3 and cleanly separated from 2 during workup of the reaction solution, was the only major byproduct from bromine oxidations in the presence of nickel(II) alkanoates.

In contrast to the selective bromine oxidations of disubstituted-1,4-butanediols, for which nickel(II) 2-ethylhexanoate does not exhibit significant advantage over nickel(II) benzoate,[13] nickel(II) 2-ethylhexanoate is markedly superior to the corresponding benzoate for selective bromine oxidations of the primary alcohol site of 4-substituted-1,4-butanediols. The enhanced oxidation of primary alcohols, relative to secondary alcohols, is presumed to result from coordinative association of nickel(II) with the diol. Oxidation of the resulting complex is then subject to steric influences from the alkanoate ligands which, in the specific case of 2-ethylhexanoate, causes an estimated minimal 100-fold increase in the relative rate for oxidation at the primary alcohol site. Electronic influences from diol substituents, as is suggested in the reduced yield of 2 when R = C_6H_5, also affect the selectivity of these oxidations.

Nickel(II) alkanoates not only enhance selectivity in alcohol oxidations but also moderate solution acidity. The hydrogen bromide that is liberated during bromine oxidations is exchanged on the nickel(II) alkanoate with resulting formation of nickel(II) bromide and the corresponding carboxylic acid.[14] This necessitates the use of excess nickel(II) alkanoate since $NiBr_2$, which competes with the alkanoate for association with the alcohol, does not provide such steric selectivity. Similar factors may account for the loss of selectivity when attempts are made to employ $RuCl_2(PPh_3)_3$ as a catalyst for diol oxidations.[11]

Experimental Section

General Oxidation Procedure. Bromine (9.0 mmol/mmol of diol) in anhydrous acetonitrile (5.0 mL/9.0 mmol of Br_2) was added dropwise to a continuously stirred mixture of diol 1 and anhydrous nickel(II) alkanoate (5.0 mmol/mmol of diol) in acetonitrile (10 mL/mmol of diol) at 25 °C over a 60-min period. The solution color was characteristically green until excess molecular bromine had been added. After a reaction time of 5 h, the reaction mixture was poured into 10% aqueous hydrochloric acid and extracted with ether. The resultant ether solution was washed with 10% aqueous hydrochloric acid, 20% aqueous sodium hydroxide, and water and then dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure provided the corresponding lactone, generally in >90% purity.

Products were characterized by standard spectral methods as well as by GC retention times (20% Carbowax 20 M columns). Yields of the isolated products were determined by GC methods, using an internal standard, benzyl ether, which was added to the reaction mixture prior to workup. Reported yields were based on duplicate runs and were reproducible to within ±2%. Keto acid 4 was the only major byproduct of these oxidations and could be isolated in 20–30% yields following a workup procedure that excluded the base washing.

Lower yields of 2 (R = C_6H_5) were obtained when reactions were performed with only 2 equiv of nickel(II) 2-ethylhexanoate (22% yield), at 0 °C (10% yield), or in methylene chloride (20% yield). Use of the nickel(II) bromide/benzoyl peroxide combi-

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(14) As a consequence, epoxides such as cyclohexene oxide are inert to ring opening and oxidation by the nickel(II) alkanoate/bromine reagent combination.

nation[12] (5:3:1 molar ratio of $NiBr_2/Bz_2O_2$/diol, R = C_6H_5) produced a complex mixture of products that included lactone **2** (20% yield) and keto alcohol **3** (9% yield).

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Registry No. **1** (R = C_6H_5), 4850-50-4; **1** (R = C_4H_9), 51916-47-3; **1** (R = C_6H_{13}), 37810-94-9; **2** (R = C_6H_5), 1008-76-0; **2** (R = C_4H_9), 104-50-7; **2** (R = C_6H_{13}), 706-14-9; nickel(II) 2-ethylhexanoate, 4454-16-4; bromine, 7726-95-6.

Synthesis of 7-Hydroxybicyclo[3.3.0]oct-8-en-2-one Derivatives and Use of Carbonate Participation for Stereospecific Epoxidation

Martin F. Haslanger* and Syed Ahmed

The Squibb Institute for Medical Research, Princeton, New Jersey 08540

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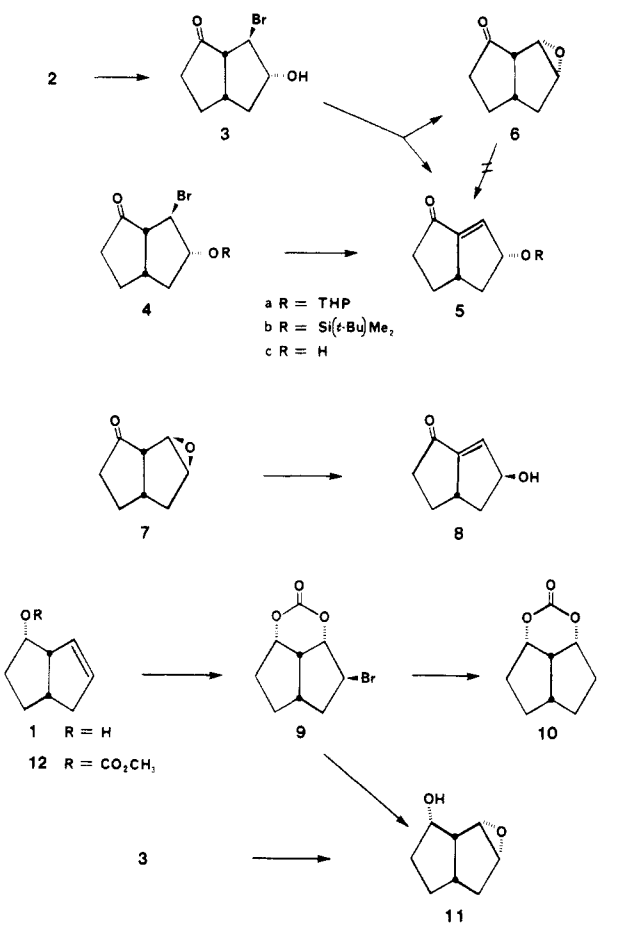
Bicyclo[3.3.0]oct-7-en-2-ol (**1**) is a readily prepared pentalene derivative which has served as the starting point of several sesquiterpene syntheses[1] and can be obtained in chiral form.[2] We[3] and others[4] have utilized this starting material to synthesize prostacyclin analogues. Bicyclo[3.3.0]octene **5** possesses functionality suitable for the stereocontrolled assembly of prostacyclin analogues[3] and sesquiterpenes such as coriolin.[5] Recent reports[6] on the preparation of enone **5** prompt us to present our work in this area. Herein we report the direct conversion of alcohol **1** to enone **5** and the introduction of a novel oxidative bromocarbonation to demonstrate its relative stereochemistry.

The enone **2** is obtained from alcohol **1** by CrO_3–pyridine oxidation.[7] Treatment of bicyclic enone **2** with *N*-

bromoacetamide in aqueous acetone gives crystalline bromohydrin **3** in 82% yield. The anticipated stereochemistry of bromohydrin **3**[8] is supported by the chemical correlation described below. Treatment of bromohydrin **3** with 1,8-diazabicyclo[5.4.0]undecene (DBU) gives a 1:1 mixture of epoxy ketone **6** and hydroxy enone **5c** (Scheme I). Epoxide **6** is not converted to enone **5c** upon further treatment with triethylamine or DBU. However, treatment of epoxy ketone **6** with sodium carbonate results in a low yield of hydroxy enone **5c**.[6b] The stability of *endo*-epoxy ketone **6** contrasts sharply with the reactivity of *exo*-epoxy ketone **7**, prepared as previously described.[6b]

Scheme I



We have found that *exo*-epoxy ketone **7** is rapidly converted to hydroxy enone **8** upon treatment with DBU or triethylamine at room temperature (Scheme I). The bromo ketone **4** and *exo*-epoxide **7** readily undergo elimination, while *endo*-epoxide **6** fragments at a notably slower rate.[9]

Protection of the hydroxyl function as either the tetrahydropyranyl ether[10] **4a** or *tert*-butyldimethylsilyl ether[11] **4b** allows dehydrobromination with DBU to proceed cleanly to give enone **5a** or **5b** in 80% yield after chromatography. In view of a previous report on the relative instability of a bridgehead double bond in bicyclo[3.3.0]-octenes,[12] it is interesting to note that no isomers of enone **5** were detected in the elimination reaction. Thus we have demonstrated that expeditious protection of the hydroxyl group of bromohydrin **3** allows straightforward conversion of ketone **2** to enone **5** in high yield without unnecessary protection and deprotection steps.[6] Synthetic sequences for the further elaboration of enone **5** will generally require hydroxyl protection.[3-5] This protection is conveniently introduced at bromohydrin **3** and, although we have used THP and *tert*-butyldimethylsilyl ethers, presumably any DBU stable protecting group could be employed.

The relative stereochemistry of pentalenone **5** is crucial to its synthetic utility. Prior to the publication of other reports[6] we sought to prove the relative configuration of

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