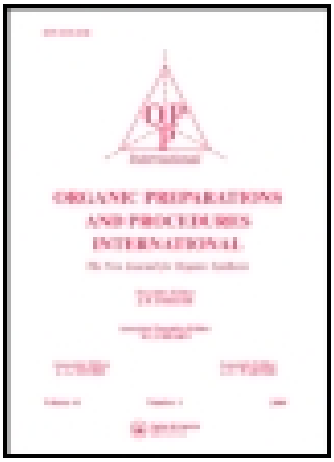

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REDUCTION AND OXIDATION OF 1-METHYLCYCLOHEXA-2,5-DIENE-1-CARBOXYLIC ACIDS

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REDUCTION AND OXIDATION OF 1-METHYLCYCLOHEXA-2,5-DIENE-1-CARBOXYLIC ACIDS

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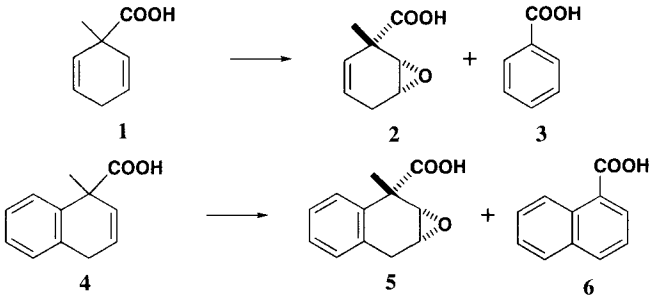
The reactivity of substituted 1,4-dienes and their use as synthetic precursors to natural products of pharmaceutical interest have been widely documented.[1-2] In a preliminary report,[2f] we showed that highly functionalized dienes obtained from a Birch alkylation reaction (BAR) of α-tetralones are extremely sensitive to various reaction conditions as well as their mode of storage. It was our interest to study the stability and behavior of 1-methylcyclohexa-2,5-diene-1-carboxylic acids (**1** and **4**) derived from a BAR of benzoic and α-naphthoic acids, in oxidation reactions with oxone® and *m*-CPBA (*Scheme 1, Table 1*) and reduction with lithium aluminum hydride (*Scheme 2 and Table 2*); there is no study reported of these diene-acids in such reactions in the literature. As was pointed out earlier for the benzoic ester and α-tetralone dienes,[2f,3] the diene-acids **1** and **4**[2c,4] remained stable for months when they were stored at –20°C under nitrogen atmosphere and, but they undergo slow decomposition at room temperature.

Epoxidation of **1** and **4**, using oxone®, H_2O, phosphate buffer, benzene-acetone and 18-crown-6 at 10°C,[5,6] provided the α-epoxides **2** and **5** as expected together with significant quantities of the aromatic carboxylic acids **3** and **6** respectively (*Scheme 1*). All reactions proceeded



Oxidation Products of the Diene-acids 1 and 2

Scheme 1

with the total consumption of the starting materials to give, after flash chromatography, 2:1 mixtures of **2** and **3** from acid **1** (85-92%) and of **5** and **6** from the acid **4** in 87-90% yields (Entries 1 and 2, *Table 1*). We next examined the reactivity with *m*-CPBA. Treatment of **1** with

m-CPBA in CH_2Cl_2 at 4°C, afforded compounds **2** and **3** (1:1 ratio, 85%); **4** gave a 1:1 mixture of **5** and **6** in 87% yield (Entries 3 and 4, *Table 1*). Reactions performed with peracid under heterogeneous conditions ($NaHCO_3$) led to a similar outcome, leading to the same products (Entries 5 and 6, *Table 1*).

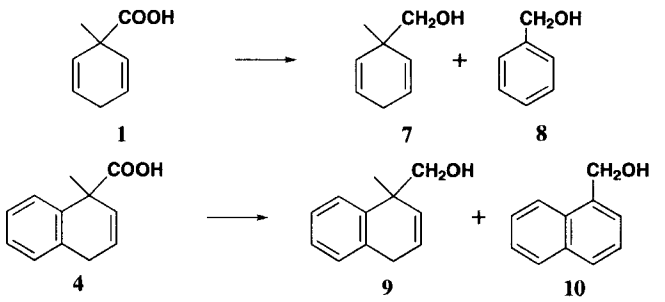
The IR and NMR spectra of **2** and **5** supported the assignment of the epoxide structures and their stereochemistry were readily determined by *NOE* measurements whereby irradiation of the methyl peak gave a nuclear *Overhauser* enhancement of the proximal epoxide and vinyl protons. In each case, the sole product was the most hindered epoxide with the oxirane oxygen located *syn* to the carboxylic group. Moreover, the use of oxone® reagent, provided the best yield of the desired epoxide (Entries 1 and 2, *Table 1*). On the other hand, in all cases, the aromatic compounds isolated were exclusively those derived from the loss of the methyl group; neither oxidative decarboxylation nor other products were detected.

Table 1. Oxidation Reaction Conditions and Product Ratios of Diene-acids **1** and **4**

Entry	Substrate	Reaction Conditions	Products (ratio,yield)
1	**1**	0.04 M $KHSO_5$, Oxone®, water-benzene-acetone, phosphate buffer pH = 7.5, 18-crown-6, 10°C, 3 h	**2:3** (2:1, 85-92%)
2	**4**	"	**5:6** (2:1, 87-90%)
3	**1**	*m*-CPBA, CH_2Cl_2, 4°C	**2:3** (1:1, 85%)
4	**4**		**5:6** (1:1, 87%) 87%
5	**1**	*m*-CPBA, 0.5 M $NaHCO_3$, CH_2Cl_2, 4°C	**2:3** (1:1, 89%)
6	**4**	"	**5:6** (1:0.8, 88%)

a) Compounds **1** and **4** for these experiments were obtained by a BAR of Benzoic and 1-Naphthoic acids.[2c]

Similarly, our attempts to reduce carboxylic acids **1** and **4** to the corresponding alcohols using lithium aluminum hydride (LAH) also produced a mixture of the alcohols **7** and **9**, and the unexpected aromatic compounds **8** and **10** from the respective acids (*Scheme 2*). We carried out



Reduction Products of the Diene-acids 1 and 4 with LAH

Scheme 2

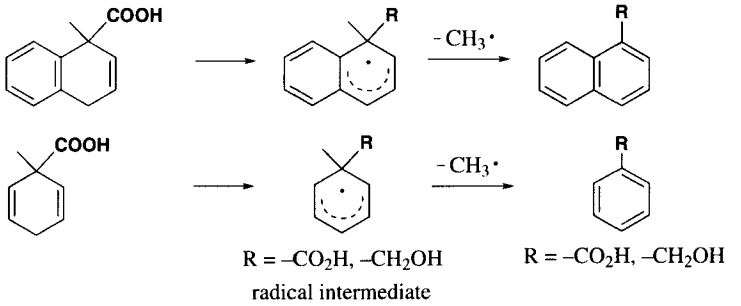
reductions under different conditions and observed that a molar ratio of 1:2 of diene to reducing agent for **1** (Entry 1, *Table 2*) and 1:4 for **4** (Entry 3, *Table 2*) were the most favorable to produce the desired diene-alcohols.

Table 2. Reduction Reaction Conditions and Product Ratios of Diene-acids **1** and **4**[a]

Entry	Substrate	Diene/LAH Ratio	Products (ratio, yield)
1	**1**	1:2	**7**:**8** (1:1, 90%)
2	**1**	1:4	**7**:**8** (1:1.5, 88%)
3	**4**	1:4	**9**:**10** (2.1:1, 88%)
4	**1**	1:7	**7**:**8** (1:1.4, 89%)
5	**1**	1:13	**7**:**8** (1:2.4, 90%)
6	**4**	1:13	**9**:**10** (1.1:1, 91%)

a) Typical experimental procedures for reduction reaction with lithium aluminum hydride in THF or Et_2O at reflux under nitrogen atmosphere were used.

We conclude that these results do not implicate thermal aromatization or rearrangement of the diene-acids to the aromatic compounds. The formation of two different products in both oxidation and reduction processes suggests a competition between different reaction mechanisms, one *polar* leading to the desired products **2**, **5**, **7**, and **9** and the other involving a *homolytic* bond fission to aromatic acids **3**, **6** and aromatic alcohols **8**, **10** with common radical intermediates as illustrated in *Scheme 3*.



Scheme 3

EXPERIMENTAL SECTION

IR spectra were determined on a Nicolet Impact Model 410 instrument. All NMR spectra were recorded in $CDCl_3$ on a Bruker Ac 200-E NMR spectrometer. Reactions were carried out under a nitrogen atmosphere. Silica gel 60 GF_{254} was used for flash chromatography under low nitrogen pressure. All solvents were dried and distilled before use.

Typical Procedure for Epoxidation

Oxone· Method.- A freshly prepared solution of oxone® (potassium peroxomonosulfate, 0.04 M, 85 mL) in water (8.5 mL) was added dropwise to a well-stirred biphasic mixture of benzene

(14.2 mL), aqueous buffer (pH = 7.5, 0.05 M phosphate buffer, 5.7 mL) kept at 4-6°C containing diene-acid **1** (1.45 mmol), acetone (1.1 mL) and 18-crown-6 (85 mg) as the phase-transfer catalyst. The pH was monitored during the addition and kept constant by means of 0.5 N KOH addition. The mixture was stirred at 10°C for 4 h. The benzene layer was then separated, and the aqueous phase was extracted with benzene. The combined organic extract was dried over anhydrous $MgSO_4$, and after removal of the solvent *in vacuo,* the residue was purified by column chromatography (silica gel, hexane-EtOAc) to afford a 92% yield of two pure products **2** (135.5 mg, 0.88 mmol) and **3** (54 mg, 0.45 mmol).

2-Methyl-7-oxabicyclo[4.1.0]hept-3-ene-2-carboxylic Acid (2): Colorless oil; IR (film): 3400, 1780 (monomer), 1720 (dimer), 1250, 1150, 1080, 920, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.56 (s, 3 H), 2.41 (m, 2 H), 4.29 (m, 1 H), 4.38 (d, *J* = 3.0 Hz, 1 H), 5.69 (br d, *J* = 10.0 Hz, 1 H), 5.93 (m, 1 H); ^{13}C NMR ($CDCl_3$ 50 MHz): δ 19.5, 27.4, 54.3, 63.6, 78.0, 129.9, 133.5, 178.3; EIMS: *m/z* 154 (M^+, 20%), 139 (30%), 95 (65%), 77 (50%), 44 (100%); CIHRMS: Calcd for $C_8H_{10}O_3$: 154.0630, Found: 172.0970 (MNH_4+).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.39; H, 6.59

m-CPBA Method.- To a solution of acid **4** (1 mmol) in 5 mL of dry CH_2Cl_2 was added *m*-CPBA (1.2 mmol) in small portions and then kept stirring at 4°C until TLC indicated complete reaction. The reaction mixture was poured into cold 0.5 M $NaHCO_3$ (5 mL) and the aqueous layer was then separated and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with water, dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography on silica gel using increasing concentrations of EtOAc in hexane to afford the pure (TLC and ^1H-NMR) products **5** (89 mg, 0.43 mmol) and **6** (75 mg, 0.43 mmol), in 87% total yield.

2-Methyl-1a,2,7,7a-tetrahydro-1-oxacyclopropa[*b*]naphthalene-2-carboxylic Acid (5): Colorless oil; IR (film): 3450, 3080, 1780, 1720, 1610, 1250, 1080, 910, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.81 (s, 3 H), 3.00 (m, 2 H), 4.35 (m, 1 H), 4.52 (d, *J* = 3.9 Hz, 1 H), 6.90-7.50 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.0, 33.4, 53.3, 67.1, 80.8, 125.8, 127.9, 128.3, 129.6, 133.2, 137.4; EIMS: *m/z* 204 (M^+, 18%), 145 (100%), 130 (45%), 115 (48%), 91 (27%); CIHRMS: Calcd for $C_{12}H_{12}O_3$: 204.0786, Found: 222.1121 (MNH_4+).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.55; H, 5.94

Reduction

Typical experimental procedures for the reaction with lithium aluminum hydride in THF or Et_2O at reflux under nitrogen atmosphere were used. Reductions were also carried out using different work-up procedures, such as basic, acid and KF media, for the extraction of the products from the reaction mixture.

(1-Methylcyclohexa-2,5-dienyl)methanol (7).- Colorless oil (56 mg, 0.45 mmol); IR (film): 3350, 3020, 1650, 1380, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.00 (s, 3 H), 2.65 (dt, *J* = 1.9, 3.3, 2 H), 3.32 (s, 2 H), 5.48 (dt, *J* = 10.4, 1.9, 2 H), 5.88 (dt, *J* = 10.5, 3.3, 2 H); ^{13}C NMR

($CDCl_3$, 50 MHz): δ 24.6, 26.3, 38.9, 70.7, 125.9, 130.9; CIHRMS: Calcd for $C_8H_{12}O$: 124.0888, Found: 142.1229 (MNH_4+).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.41; H, 9.80

(1-Methyl-1,4-dihydronaphthalen-1-yl)methanol (9): Pale yellow oil (104.4 mg, 0.6 mmol); IR (film): 3350, 3020, 2850, 1630, 1380, 1030, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.34 (s, 3 H), 3.43 (br s, 2 H), 3.55, 3.70 (AB system, 2 H), 6.10 (dt, J = 3.6 and 12.0 Hz, 1 H), 5.60 (dt, J = 3.6 and 10.9 Hz, 1 H), 7.16-7.24 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.4, 30.1, 41.2, 71.9, 126.0, 126.3, 125.4, 125.7, 128.3, 132.5, 134.7, 139.2; CIHRMS: Calcd for $C_{12}H_{14}O$: 174.1045, Found: 192.1384 (MNH_4+).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H , 8.10. Found: C, 82.70; H, 8.00

Alcohols **8** and **10** are known compounds and were identified by their spectral data.[7,8]

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8. Beilstein, **6**, 667.

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REDUCTIVE THIOLATION APPROACH TO PURE CYCLOBUTYL PHENYL SULFIDE

Submitted by (11/10/04) Matthew C. T. Fyfe* and Chrystelle M. Rasamison

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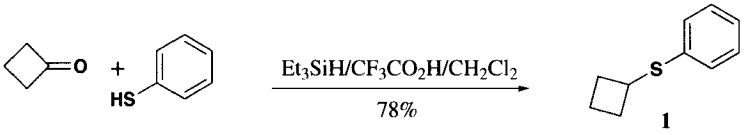
Cyclobutyl phenyl sulfide (**1**) is a precursor of cyclobutyl phenyl sulfoxide, a reagent extremely useful for the synthesis of spirocyclic cyclopentanones.[1a] In our laboratories, we required a method for the large scale production of **1**, a compound necessary for the construction of a range of potent glucokinase activators (GKAs)[2] that could form the basis of a treatment for type 2 diabetes. Here, we discuss how the difficulties associated with previous syntheses[1] of **1** were overcome by the development of a novel synthetic route that relies upon a modified reductive thiolation[3] protocol.



1

Two approaches have previously been employed for the synthesis of **1**, *viz.*, the radical addition of thiophenol to bicyclo[1.1.0]butane[1b] and the alkylation of sodium thiophenolate with cyclobutyl bromide.[1a] The first of these approaches was not attempted because of the difficulties associated with procuring large quantities of bicyclo[1.1.0]butane.[4] Moreover, the second of these approaches, involving the reaction of thiophenolate with cyclobutyl bromide, did not proceed as planned. In this instance, an 85% yield of a mixture, comprising the desired thioether **1** (89%) and cyclopropylmethyl phenyl sulfide (**2**, 11%), was obtained. The starting cyclobutyl bromide, purchased from Aldrich (Catalogue no.: 22,699-8), contained 6% cyclopropylmethyl