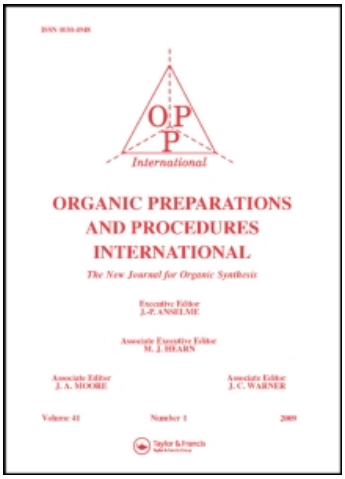


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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

Liliana E. Luna[a]; Raquel M. Cravero[a]
[a] Departamento de Química Orgánica, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario-Suipacha, Instituto de Química Orgánica de Síntesis, Rosario, ARGENTINA

To cite this Article Luna, Liliana E. and Cravero, Raquel M.(2005) 'REDUCTION AND OXIDATION OF 1-METHYLCYCLOHEXA-2,5-DIENE-1-CARBOXYLIC ACIDS', Organic Preparations and Procedures International, 37: 2, 189 — 194
To link to this Article: DOI: 10.1080/00304940509354886
URL: http://dx.doi.org/10.1080/00304940509354886

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

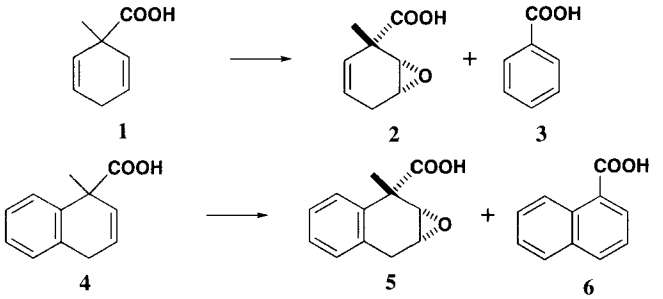
Submitted by (11/04/04) Liliana E. Luna and Raquel M. Cravero*

Instituto de Química Orgánica de Síntesis, Departamento de Química Orgánica, Facultad de Ciencias Bioquímicas y Farmacéuticas Universidad Nacional de Rosario-Suipacha 531 S2002LRK Rosario, ARGENTINA

Tel./ Fax: 54-341-4370477, e-mail: rcravero@fbioyf.unr.edu.ar

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*).

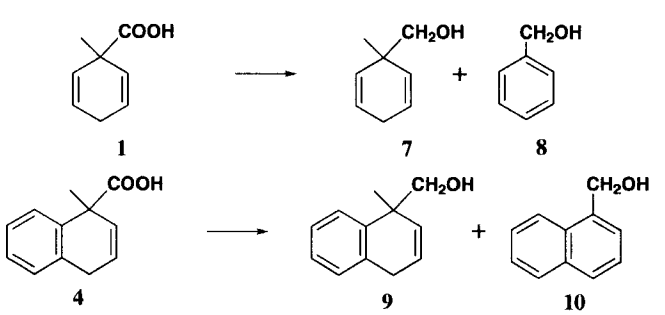
The IR and NMR spectra of **2** and **5** supported the assignment of the epoxide structures and their stereochemistry were readily determined by *NOE* measurements whereby irradiation of the methyl peak gave a nuclear *Overhauser* enhancement of the proximal epoxide and vinyl protons. In each case, 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

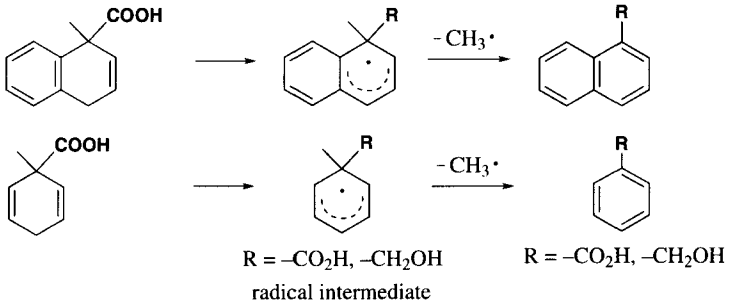
reductions under different conditions and observed that a molar ratio of 1:2 of diene to reducing agent for **1** (Entry 1, *Table 2*) and 1:4 for **4** (Entry 3, *Table 2*) were the most favorable to produce the desired diene-alcohols.

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]

Acknowledgments.- The authors wish to acknowledge the support of UNR (Universidad Nacional de Rosario) and CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas), for financial support

REFERENCES

1. a) G. A. Russell, *J. Chem. Ed.*, **59**, 1112 (1963). b) J. A. Howard, K. U. Ingold and *Can. J. Chem.*, **45**, 785 (1967). c) D. G. Hendry and D. J. Schuetzle, *Am. Chem. Soc.*, **97**, 7123 (1975). d) A. J. Baker and A. C. Goudie, *J. Chem. Soc. Chem. Comm.*, 951 (1972). e) A. G. Schultz, R. E. Harrington and F. S. Tham, *Tetrahedron Lett.*, **33**, 6097 (1992). f) A. G. Schultz, A. G. Taveras and R. E. Harrington, *Tetrahedron Lett.*, **29**, 3907 (1988). g) S. Arseniyadis, D. V. Yashunsky, R. Pereira de Freitas, R. Brondi-Alves, M. Muñoz Dorado, Q. Wang and P. Potier, *Tetrahedron Lett.*, **35**, 9395 (1994). h). D. J. Hart, H. Chih Huang, R. Krishnamurthy and T. Schwartz, *J. Am. Chem. Soc.*, **111**, 9136 (1989). i) A. G. Schultz, R. E. Harrington, M. Macielag, P. G. Mehta and A. G. Taveras, *J. Org. Chem.*, **52**, 5482 (1987).

2. a) A. J. Vila, R. M. Cravero and M. Gonzalez Sierra, *Tetrahedron Lett.*, **32**, 1929 (1991). b) A. J. Vila, R. M. Cravero and M. Gonzalez Sierra, *Tetrahedron*, **49**, 4511 (1993). c) A. G. Lo Cascio, G. R. Labadie, M. Gonzalez Sierra and R. M. Cravero, *Org. Prep. Proced. Int.*, **32**, 298 (2000). d) G. R. Labadie, R. M. Cravero and M. Gonzalez Sierra, *Synthetic Commun.*, **30**, 4065 (2000). e) G. R. Labadie, R. M. Cravero and M. Gonzalez Sierra, *Synthetic Commun.*, **26**, 4671 (1996). f) G. R. Labadie, G. Estiú, R. M. Cravero and M. Gonzalez Sierra, *Theochem*, **635**, 173 (2003). g) G. R. Labadie, L. E. Luna, M. Gonzalez Sierra and R. M. Cravero, *Eur. J. Org. Chem.*, 3429 (2003).

3. A. L. J. Beckwith, D. M. O' Shea and D. H. Roberts, *J. Am. Chem. Soc.*, **108**, 6408 (1986).

4. B. Ganem, G. W. Holbert, L. B. Weiss and K. Ishizumi, *J. Am. Chem. Soc.*, **100**, 6483 (1978).

5. W. Adam, R. Curci, L. D'Accolti, A. Dinoi, C. Fusco, F. Gasparrini, R. Kluge, R. Paredes, M. Schultz, A. K. Smerz, L. A. Veloza, S. Weinkotz and R. Winde, *Chem. Eur. J.*, **3**, 105 (1997).

6. R. Curci, M. Fiorentino, L. Troisi, J. O. Edwards and R. H. Pater, *J. Org. Chem.*, **45**, 4758 (1980).

7. Beilstein, **6**, 428, Merck Index, **12**, 1159.

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

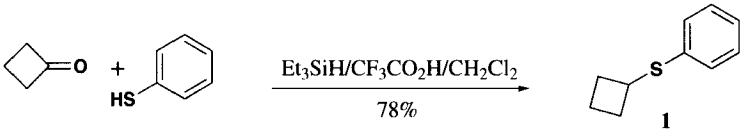
****

REDUCTIVE THIOLATION APPROACH TO PURE CYCLOBUTYL PHENYL SULFIDE

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

Prosidion Ltd, Watlington Road, Oxford, Oxon OX4 6LT, UK
e-mail: mfyfe@prosidion.com

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