

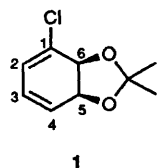
New Cycloaddition Chemistry of 1-Chloro-5,6-*cis*-isopropylidenedioxycyclohexa-1,3-diene Derived from the Oxidation of Halogenobenzenes by *Pseudomonas putida* 39D

Tomas Hudlicky* and Bryan P. McKibben

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA

Several new modes of cycloadditions of 1-chloro-5,6-*cis*-isopropylidenedioxycyclohexa-1,3-diene **1** have been investigated. Under thermal conditions, benzoquinone, naphthoquinone and benzyne react with **1** to give [4 + 2] cycloadducts resulting from addition to the less hindered face and in an *endo* fashion. Under photolysis conditions, benzoquinone undergoes a hetero [4 + 2] cyclization with the diene. Generation of nitrile oxide in the presence of the diene leads to a stereoselective [3 + 2] cycloaddition.

In 1970, Gibson *et al.*¹ reported the microbial oxidation of benzene (and derivatives) to cyclohexadiene-*cis*-diols by the mutant strain *Pseudomonas putida* 39D. These chiral synthons have been used in the enantioselective synthesis of many natural products.² Cycloadditions of the cyclohexadiene-*cis*-diols or

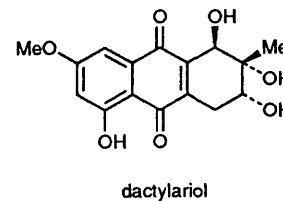
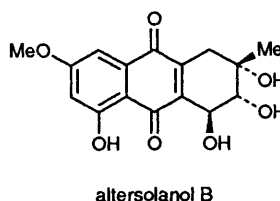
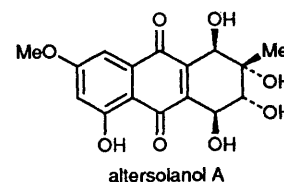
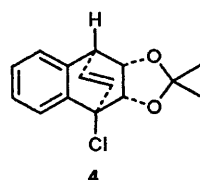
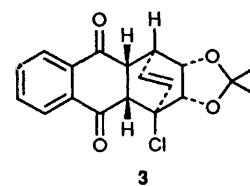
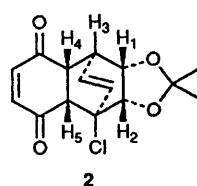


their acetonides **1** with a variety of dienophiles, for example, dimethyl acetylenedicarboxylate,³ *N*-ethylmaleimide,⁴ *N*-phenylmaleimide,⁵ ketene^{6,7} and acyl nitroso compounds have been investigated. The latter reaction has been used extensively in the synthesis of aminocyclitols.⁸⁻¹⁰ Similarly, [2 + 1]^{6,7,11} and [2 + 2]⁶ cycloadditions to the more electron rich C-4 and C-5 olefin were reported. Results were consistent with predictions based on molecular orbital calculations (AM1, MOPAC).^{12,13} In this paper we report on some new applications of the cycloaddition protocol with potential in the synthesis of anthraquinone type antibiotics and novel heterocyclic compounds.

Results and Discussion

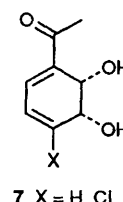
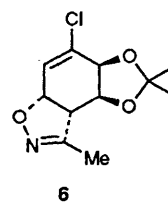
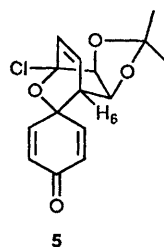
Generation of benzyne in the presence of **1** gave the expected cycloadduct **4** (66%).¹⁴ 1-Chloro-5,6-*cis*-isopropylidenedioxycyclohexa-1,3-diene **1** underwent a thermal Diels-Alder reaction with benzoquinone and naphthoquinone to yield cycloadducts **2** (53%) and **3** (40%). The nuclear Overhauser effects (NOE) of **2** and **3** indicated that both quinones react from the less hindered face and in an *endo* manner. In the NOE studies of **2**, irradiation of 1-H shows enhancement of 3-H, 4-H and 5-H, which is only possible in the *endo* structure. Cycloadduct **3** showed a similar NOE enhancement. Ozonolysis of **3** would yield a tricyclic framework similar to and possibly convertible into the anthraquinone type antibiotics altersolanol A, B and dactylariol.^{15,16}

Photolysis of benzoquinone and **1** in benzene produced the hetero Diels-Alder adduct **5** (16%) as a single regioisomer. Benzoquinone has been shown to undergo hetero [4 + 2] cycloadditions in the presence of a diene under photolytic conditions.¹⁷ Regioselectivity was proven by heteronuclear multibond correlation (HMBC). This 2D-NMR technique showed that the spirocyclic carbon of the quinone is no greater



than 3 carbons away from the carbon bearing 6-H. This feature is evident in **5** but not in the other possible regioisomer.

The reaction of 1-chloro-5,6-*cis*-isopropylidenedioxycyclohexa-1,3-diene with nitrile oxide (derived from nitroethane)^{18,19} yielded stereoselectively the bicyclic compound **6** (73%). The regioselectivity of nitrile oxide addition was proven by NMR decoupling experiments. It should be noted that a series of simple steps (hydrogenation; Nef reaction; elimination) should yield diols **7**, attainable in only one enantiomeric configuration



7 X = H, Cl

from microbial oxidation of acetophenone by *P. putida* 39D.²⁰ Attempts at intermolecular [4 + 4] cycloadditions of **1** under

thermal, photochemical²¹ and nickel catalysed^{22–24} conditions failed because of aromatization of the cyclohexadiene-*cis*-diol **1**.

As far as we are aware, these results represent the first examples of cycloadditions of quinones or nitrile oxides to homochiral cyclohexadiene-*cis*-diols such as **1**. These compounds remain homochiral because of the presence of the halogen atom and will find use in the construction of anthraquinone type antibiotics and other natural products. We will report on these and other endeavours in due course.

Experimental

A Cycloaddition Procedure.—*Diels–Alder adduct 4 of 1-chloro-5,6-cis-isopropylidenedioxycyclohexa-1,3-diene 1 with benzyne.* To a two-necked flask fitted with an addition funnel and a reflux condenser was added a solution of **1** (562 mg, 3.01 mmol) dissolved in dimethoxyethane (DME, 5.5 cm³). Isopentyl nitrite (960 mg, 8.2 mmol) was added and the reaction mixture was brought to reflux. A solution of anthranilic acid (1.425 g, 10.4 mmol) dissolved in DME (5.5 cm³) was added dropwise over a period of 20 min to the refluxing solution. After the addition was complete the solution was refluxed for another 40 min. The reaction was cooled to room temperature, diluted with Et₂O (25 cm³) and washed with a 5% aq. NaOH. The aqueous layer was extracted with Et₂O (3 × 25 cm³). The combined organic layers were dried over MgSO₄ and concentrated at reduced pressure. Chromatography (silica, hexane–EtOAc, 25:1) yielded *Diels–Alder adduct 4* as a pale yellow oil (521 mg, 66%), *R*_f 0.18 (hexane–EtOAc, 25:1); $[\alpha]_D^{25}/10^{-1}$ deg cm² g⁻¹ + 59.7 (*c* 0.83, CHCl₃); $\nu(\text{neat})/\text{cm}^{-1}$ 2995, 2940, 1620, 1470, 1270 and 1100; $\delta_{\text{H}}(\text{CDCl}_3)$; *J*(Hz) 1.28 (s, 3 H), 1.44 (s, 3 H), 4.13 (m, 1 H), 4.22 (dd, 1 H, *J* 7.0, 1.2), 4.36 (ddd, 1 H, *J* 7.1, 3.6, 1.1), 6.43 (m, 2 H), 7.22 (m, 3 H) and 7.64 (m, 1 H); $\delta_{\text{C}}(\text{CDCl}_3)$ 25.3, 25.7, 44.6, 71.7, 79.7, 84.5, 113.0, 123.0, 124.3, 126.6, 127.1, 132.0, 136.2, 137.6 and 139.6; *m/z* (CI, 70 eV) (rel. intensity) 263 (*M* + 1) (25), 247 (20), 233 (15) and 205 (100) [Found: C, 68.5; H, 5.8%; *M* + H, 263.0843 (error 1.7 ppm). Calc. for C₁₅H₁₅ClO₂: C, 68.57; H, 5.75%; *M* + H, 263.0839].

Acknowledgements

We thank Genencor International, for financial support.

References

- 1 D. Gibson, M. Hensley, H. Yoshioka and T. Mabry, *Biochemistry*, 1970, **9**, 1626.
- 2 For recent reviews see: (a) T. Brown and T. Hudlicky, in *Organic Synthesis: Theory and Applications*, ed. T. Hudlicky, JAI Press, Greenwich, CT, 1993, vol. 2, p. 113; (b) D. Ribbons and D. Widowson, *Janssen Chim. Acta*, 1990, **8**, 3; (c) H. Carless, *Tetrahedron: Asymmetry*, 1992, **3**, 795.
- 3 J. Williams, S. Roberts and I. Cotterill, *J. Chem. Soc., Chem. Commun.*, 1988, 1629.
- 4 J. Williams, S. Roberts, C. Pittol, R. Pryce, G. Ryback and V. Sik, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1160.
- 5 D. Burnell and J. Gillard, *J. Chem. Soc., Chem. Commun.*, 1989, 1439.
- 6 J. Williams, S. Roberts, W. Downing, R. Latouche, C. Pittol, R. Pryce and G. Ryback, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2613.
- 7 M. Mahon, K. Molloy, C. Pittol, R. Pryce, S. Roberts, G. Ryback, V. Sik, J. Williams and J. Winders, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1255.
- 8 O. Werbitzky, K. Klier and H. Felber, *Liebigs Ann. Chem.*, 1990, 267.
- 9 W. Piepersberg, B. Beier and K. Schurrle, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2407.
- 10 T. Hudlicky and H. Olivo, *Tetrahedron Lett.*, 1991, **32**, 6077.
- 11 M. Banwell and M. Collins, *J. Chem. Soc., Chem. Commun.*, 1991, 1343.
- 12 T. Hudlicky, J. Price, F. Rulin and T. Tsunoda, *J. Am. Chem. Soc.*, 1990, **112**, 9439.
- 13 T. Hudlicky, F. Rulin, T. Tsunoda, H. Luna, C. Anderson, T. Nugent and J. Price, *Isr. J. Chem.*, 1991, **31**, 229.
- 14 Benzyne additions have been investigated previously by M. Banwell (University of Melbourne), personal communication.
- 15 G. Assante and G. Nasini, *Phytochemistry*, 1987, **26**, 703.
- 16 K. Krohn, H. Markus, H. Kraemer and W. Frank, *Liebigs Ann. Chem.*, 1988, 1033.
- 17 J. Baltrop and B. Hesp, *J. Chem. Soc.*, 1965, 5182; U. Burger, P.-A. Lottaz, P. Millason and G. Bernardinelli, *Helv. Chim. Acta*, 1994, **77**, in the press.
- 18 T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 1960, **82**, 5339.
- 19 A. Baco, S. Benetti, G. Pollini, P. Baraldi, M. Guarneri, D. Simoni and C. Gandolfi, *J. Org. Chem.*, 1981, **46**, 4518.
- 20 D. Gibson, B. Gschwendt, W. Yeh and V. Kopal, *Biochemistry*, 1973, **12**, 1520.
- 21 S. Sieburth and J. Chen, *J. Am. Chem. Soc.*, 1991, **113**, 8163.
- 22 P. Wender and N. Ihle, *J. Am. Chem. Soc.*, 1986, **108**, 4678.
- 23 P. Wender, N. Ihle and C. Correia, *J. Am. Chem. Soc.*, 1988, **110**, 5904.
- 24 P. Wender and M. Tebbe, *Synthesis*, 1991, 1089.

Paper 4/00072B

Received 6th January 1994

Accepted 14th January 1994