Microbial Oxidation of Aromatics in Enantiocontrolled Synthesis. 3.[1] Design of Amino Cyclitols (*exo*-Nitrogenous) and Total Synthesis of (+)-Lycoricidine via Acylnitrosyl Cycloaddition to Polarized 1-Halo-1,3-cyclohexadienes[2]

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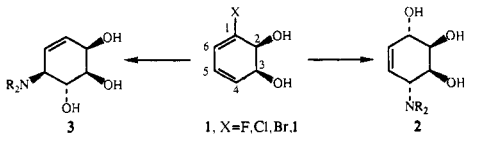
Abstract: Oxidation of halogenated benzenes with bacterial dioxygenase from *Pseudomonas putida* 39D (whole cell fermentation) provided homochiral 1,3-cyclohexadiene-*cis*-diols **1** for the entire halogen series. These compounds were investigated for their potential in cycloadditions with various dienophiles including propiolate, acylnitroso compounds, benzyne, quinones, and nitrile oxides. All cycloadducts formed with the regiochemistry predicted from molecular modeling. A brief synthesis of (+)-lycoricidine concluded the application of acylnitroso cycloadditions. New adducts of quinones and nitrile oxides were identified, and potential for these compounds in the synthesis of novel polycyclic oxygenated compounds is indicated. Experimental and spectral data are provided for all compounds.

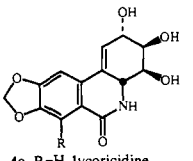
Introduction

In a recent report[1a] and in the preceding paper,[1b] we have outlined elements of design that permit the conversion of cyclohexadiene-*cis*-diols **1** to cyclitols, inositols, furanose or pyranose carbohydrates, and the aza analogs of these two types of sugars, respectively. To execute an equally efficient design of amino cyclitols, it is necessary to provide a methodology that incorporates nitrogen onto the periphery of **1** in a regio- and stereocontrolled fashion. Amino cyclitols of type **2** or **3**, or conduramines, constitute an important class of compounds, some which exhibit properties remarkably similar to those of known glycosidase inhibitors derived from aza sugars.[3,4] Their syntheses

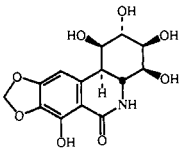


(1)

can be approached, as outlined in eq 1, by either *trans*-1,2 or *cis*-1,4 introduction of the amino and hydroxyl groups. To this end, epoxide opening with nitrogen nucleophiles can be utilized toward the preparation of compounds of type **3**, as described in the previous paper,[1b] whereas nitrosyl cycloaddition[5-7] provides the 1,4-disposition of substituents in **2**. In this paper we report on the cycloaddition of various dienophiles to polarized 1-halo-1,3-dienes **1** (X = F, Cl, Br, I) or their protected derivatives in an effort to determine electronic trends in these dienes and thence to apply this strategy to a concise synthesis of (+)-lycoricidine (**4a**),[8,9] an important congener of the cancerostatic alkaloid pancratistatin (**5**),[10-13] for which this synthesis serves as a model study.



4a, R=H, lycoricidine
4b, R=OH, narciclasine



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Results and Discussion

The enormous potential of 1-halo-1,3-cyclohexadiene-*cis*-diols in enantioselective synthesis has been amply demonstrated, as evidenced by the number of reviews in this area.[14] Figure 1 shows a number of useful chiral synthons derived from the protected chlorobenzenediol **6b**. The diversity of transformations that this metabolite can undergo allows the preparation of many valuable building blocks for asymmetric synthesis. The original discovery and isolation of the diol derived from toluene by Gibson[15] more than 25 years ago has led to the present commercial availability

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(1) (a) For the first part of this series, see: Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachmann, B.; Dudding, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553-1568. (b) For the second part, see: Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) For preliminary accounts of this work, see: (a) Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077. (b) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. (c) Hudlicky, T.; McKibben, B. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, in press.

(3) (a) For general references, see: *The Amino Sugars: the Chemistry and Biology of Compounds Containing Aminosugars*; Jeanloz, R. W., Balazs, E. A., Eds.; Academic Press: New York, 1965-1966; Vols. IA, IB, IIA, IIB. (b) Nishimura, Y. In *Studies in Natural Products Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, Part F, p 495. (c) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *28*, 319. (d) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171.

(4) For reviews on conduritols, see: (a) Balci, M.; Sutbeyaz, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715. (b) Hudlicky, T.; Cebulak, M. *Cyclitols and their Derivatives: A Handbook of Physical, Spectral, and Synthetic Data*; VCH: New York, 1993.

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(7) For applications of the nitrosyl cycloaddition in the synthesis of natural products, see: (a) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (b) Keck, G. E. *Tetrahedron Lett.* **1978**, 4767. (c) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2431. (d) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5535. (e) Kresze, G.; Dittel, W. *Liebigs Ann. Chem.* **1981**, 610. (f) Braun, H.; Burger, W.; Kresze, G.; Schmidtchen, F. P.; Vaerman, J. L.; Viehe, H. G. *Tetrahedron: Asymmetry* **1990**, *1*, 403. (g) Shishido, Y.; Kybayashi, C. *J. Org. Chem.* **1992**, *57*, 2876.

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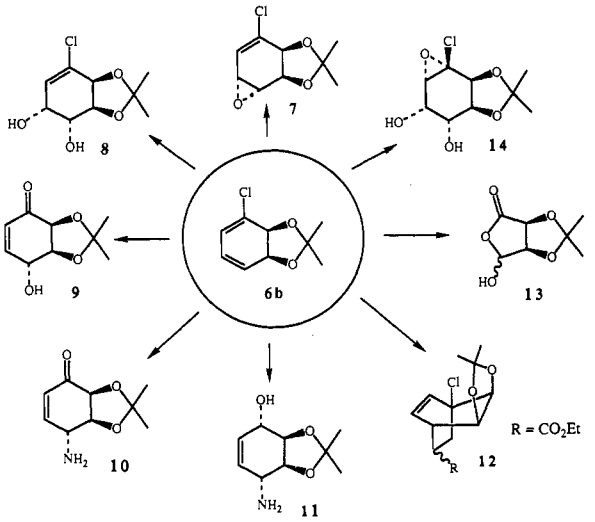
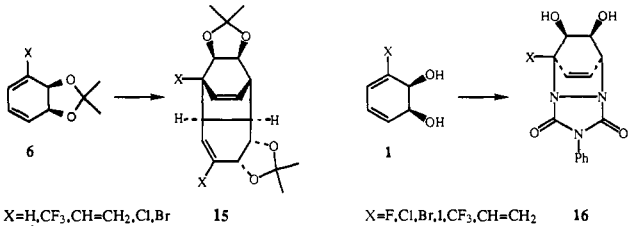


Figure 1. Some chiral synthons derived from chlorobenzene.

of many of the diols.[16] Oxidation products **8** and **14** have been converted to D-*chiro*-inositol.[17] Epoxide **7** has served as an intermediate for (−)-pinitol synthesis.[18] Lactone **13**[19] has been used in the synthesis of an isostere for renin inhibitors,[20] and ketones **9** and **10** have found use in the preparation of cyclitols[21] and conduramines.[2,21] This article examines the details of the synthesis and use of conduramine synthons **11** and bicyclo[2.2.2]-octanes **12**, attained via the Diels–Alder reaction.

We became interested in the cycloaddition potential of the 1-halodiene unit in **1** in order to prepare a bridged bicyclic system. The cycloaddition potential of polarized dienes such as **1** or **6** had not been realized until recently, although heteroatom-substituted dienes of the Danishefsky type have been amply used in synthesis.[22] Simultaneously, Roberts,[23] Ley,[24] and Hudlicky[25] have reported dimerization tendencies of acetonide derivatives of several diene diols, including those derived from bromobenzene, chlorobenzene, and (trifluoromethyl)benzene. Recently, acetonides of the diol derived from styrene have been reported to form several dimers stereoselectively.[26] The free diols also undergo Diels–Alder reaction with phenyltriazolines,[27,28] and this observation has allowed determination of the absolute stereochemistry of several diols by either X-ray or NMR methods by relying on differential shifts of diastereomeric Mosher esters derived from **16**.[27]



Surprisingly, all of the reported dimerizations were highly regio- and stereoselective; this phenomenon was explained by a less crowded transition state (anti addition) leading to **15**. The regioselectivity of the cycloaddition can easily be rationalized by the vastly different electron content of the two olefins in either **1** or **6**, which can be understood by analyzing the charge

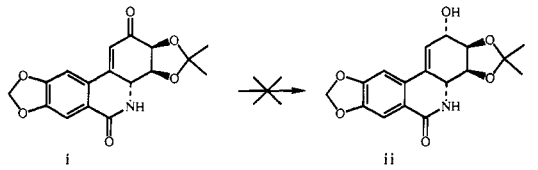


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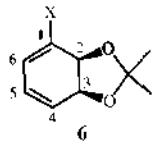
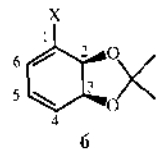
Table 1. Charge Distribution for Halobenzene-*cis*-diol Acetonides[29]



6

compd	X	C1	C6	C5	C4
6a	F	0.0622	**–0.1750**	–0.1084	0.1700
6b	Cl	–0.1024	–0.1233	–0.1272	–0.1629
6c	Br	–0.1980	–0.0838	–0.1361	–0.1437
6d	I	–0.2945	–0.0686	–0.1419	–0.1384

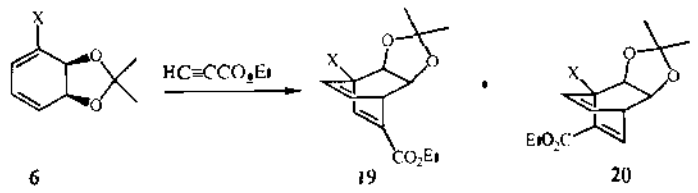
Table 2. HOMO Coefficients for Halobenzene-*cis*-diol Acetonides[29]



6

compd	X	C1	C6	C5	C4
6a	F	0.502	0.465	–0.359	–0.516
6b	Cl	0.504	0.441	–0.354	–0.498
6c	Br	0.498	0.417	–0.348	–0.473
6d	I	–0.493	–0.396	0.350	0.465

Table 3. Cycloadditions of Ethyl Propiolate

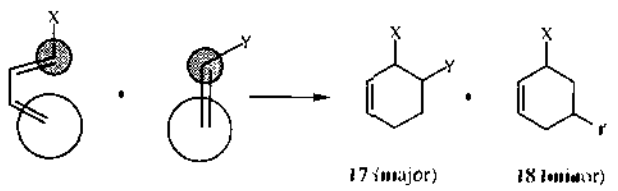


6 19 20

compd	X	**19**:**20**	yield (%)
6a	F	40:60	78
6b	Cl	55:45	40
6c	Br	35:65	61
6d	I	38:62	54

distribution of the carbon atoms in the polarized diene unit for the entire halogen series, as shown in Table 1.

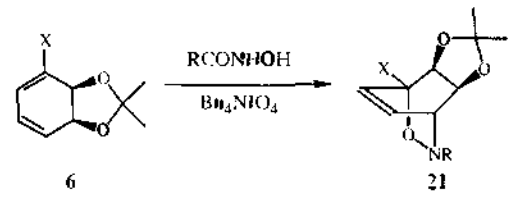
Prediction of regiochemistry according to the frontier molecular orbital theory (Table 2) would establish the "ortho" adducts **17** as expected major products over the "meta" adducts **18** in cases where X is either an electron-donating or an electron-withdrawing group.



For our study we chose two series of dienophiles—ethyl propiolate to represent a polarized carbon-containing dienophile and acylnitroso compounds to establish the results for a highly polarized heterodienophile. The results of the cycloadditions of ethyl propiolate are shown in Table 3. The reactions were performed in refluxing benzene solution for 24–48 h, and results indicate stereospecific addition with poor regioselectivity with respect to ortho and meta adducts. The expected major product, ortho adduct **20**, predominated in all cases except that of chlorobenzene-*cis*-diol by ~3:2 margin. The isomers were separated by flash chromatography and identified by NMR spectroscopy. The signal for the β-proton of the acrylate moiety appears as a singlet at δ 6.8–7.0 in adducts **19** because of additional deshielding by the halogen atoms. It appears as a doublet (J = 7 Hz) in regioisomers **20**.

(29) We thank Professor James Tanko (Virginia Tech) for his help with AM1 calculations (MOPAC, version 5.0, developed by Dewar).

Table 4. Cycloadditions of Nitrosyl Compounds

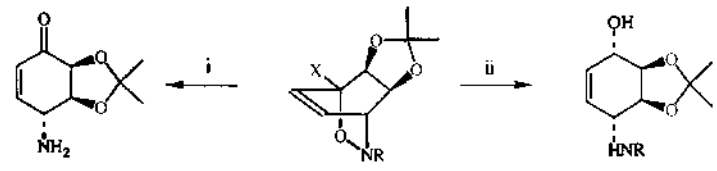


6 21

compd	X	R	product	yield (%)
6a	F	CBz[a]	**21a**	24
6b	Cl	CBz	**21b**	54
6c	Br	CBz	**21c**	74
6c	Br	Bz[b]	**21d**	70
6c	Br	Ac[c]	**21e**	51
6c	Br	*o*-Br-piperonyl	**21f**	80

[a] Cbz, benzyloxycarbonyl. [b] Bz, benzoyl. [c] Ac, acetyl.

Scheme 1

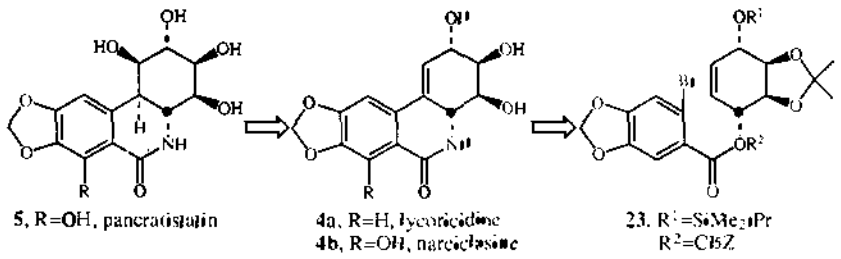


23 21 22a, R = CBz
22b, R = H

[a] Reagents: (i) Bu_3SnH, AIBN, toluene; (ii) Al(Hg), THF, H_2O.

The addition of nitrosyl dienophiles was found to be both stereo- and regiospecific. Table 4 lists the results of additions with acylnitroso compounds generated in situ from *N*-hydroxyurethane and $Bu_4N^+IO_4^-$ in the presence of the diene derivatives; in most cases the yields were quite good (>70%). The oxazine adducts were reduced to the corresponding conduramines by Keck's procedure.[2a,30] Under carefully controlled conditions, amino ketones such as **23** could be generated selectively. This type of methodology provided for easy and concise synthesis of conduramine **22b** and allowed an extrapolation to the preparation of a more complex amino cyclitol, lycoricidine, as a prelude to a general approach to the narcissus alkaloids.

Synthesis of (+)-Lycoricidine. The application of acylnitroso cycloaddition chemistry to the synthesis of lycoricidine appeared viable in view of the demonstrated success with regiochemical generation of conduramine units of type **21a–f**.[2] Thus oxazine **21f** from the reaction of (*o*-bromopiperonyl)hydroxamide with **6c** was reduced to conduramine. **22b** was protected with isopropyldimethylsilyl chloride, yielding **23**, the precursor for the Heck cyclization.[31] This compound was also prepared from



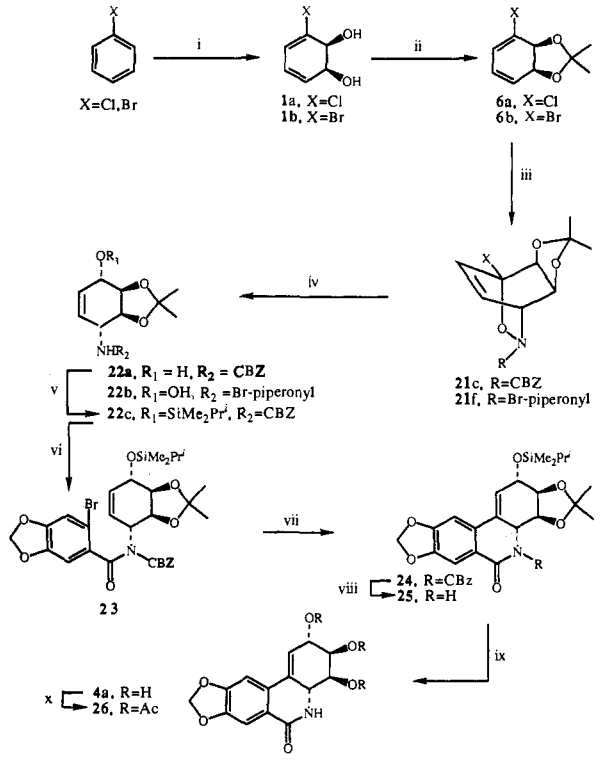
5, R=OH, pancratistatin 4a, R=H, lycoricidine
4b, R=OH, narciclasine
23, R1=SiMe2iPr
R2=CbZ

22a by acylation with bromopiperonyl chloride, followed by protection with isopropyldimethylsilyl chloride (Scheme 2) according to the procedure published by Piepersburg.[6a] Since the original report of cyclization of an isomer of **23** to the lycoricidine skeleton by Chida,[9a] several investigators have reported success with this unusual closure.[8g,9h] In our initial communication,[2b] we described technical difficulties in reproduc-

(30) For oxazine reduction, see: Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.

(31) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.3. (b) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.4.

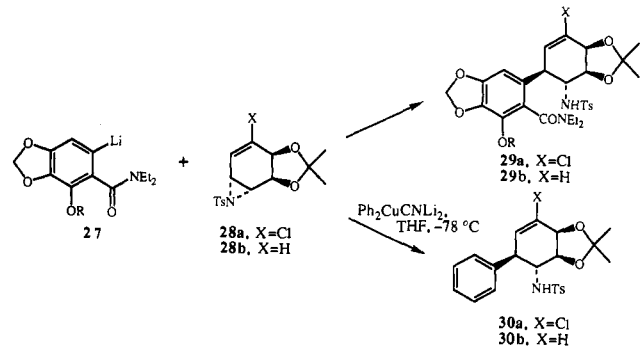
Scheme 2



[a] Reagents: (i) *P. putida*; (ii) DMP, acetone p-TsOH; (ii) RONHOH (where R = CBz or α-bromopiperonyl), $Bu_4H^+IO_4^-$, CH_2Cl_2; (iv) Al(Hg), THF, H_2O; (v) $ClSiMe_2Pri$, imidazole, DMF; (vi) BuLi, THF, than α-bromopiperonyl chloride; (vii) $Pd(OAc)_2$, DIPHOS, anisole; (viii) Pd/C, cyclohexene; (ix) CF_3CO_2H, 0 °C; (x) Ac_2O, pyridine.

ing Chida's conditions.[32] We attributed our hardship to different catalysts, but we finally succeeded when the reaction was run in anisole, an unusual solvent for this kind of reaction.[33] The lycoricidine skeleton **24** and **25** was thus attained. Since the publication of our synthesis, several groups have reported identical chemistry as well as reproducible conditions for the so-called "abnormal Heck cyclization".[31,33] (Perhaps such closures should no longer be referred to as abnormal.) Martin produced racemic lycoricidine by the use of the meso diol derived from benzene[9h] and by employing the same cyclization reported by Chida.[9a] With the acquision of **24**, the synthesis of lycoricidine was formally completed. Weinreb recently acquired the permethylated analog of **4a** via Heck cyclization of a protected conduramine.[8g] Deprotection of the D-ring protecting group gave lycoricidine **4a** in a total of nine steps from chlorobenzene, the shortest synthesis to date. An approach to pancratistatin initially modeled after the lycoricidine synthesis was abandoned because a more lucrative one was conceived that would rely on the attachment of the oxygenated aromatic unit **27**, the synthesis of which has been reported by Heathcock,[34] to an azabicyclo[4.1.0]heptene **28**.

In recent model studies, **28a** and **28b** were prepared[35] and their reactive tendencies toward nucleophilic opening were examined.[36] On treatment with diphenyl cuprate and CuCN in THF,[37] **28b** gave tosylamide **30b**. The detailed investigation of nucleophilic



opening of vinylaziridines is almost completely absent in the literature,[38] even though reports on cuprate additions to aziridines exist.[39] Attainment of **30b** bodes well for approaching pancratistatin by means of this strategy and, to our knowledge, represents the first example of nucleophilic opening of a simple vinylaziridine with a carbon nucleophile. We will report on the progress toward the total synthesis of pancratistatin as well as on the results of a complete study of the receptiveness of substrates such as **28** toward carbon nucleophiles in the near future.

Cycloaddition with Other Dienophiles. The literature contains examples of cycloadditions of propiolates, maleic anhydride, maleimide, acylnitroso compounds, and ketene to the diene diols. Efforts by Roberts,[23] Boyd,[27] and Pieperberg[6a] in this area have led us to consider the use of other dienophiles in order to expand the repertoire of cycloadducts. There is only one report of cycloadditions with benzyne,[40] and there is no record of quinone cycloadditons in the literature. Shown in Scheme 3 are the results of preliminary experiments in this new area.[2c] Diene **6a** reacted smoothly with benzyne generated in situ to provide adduct **31** in 66% yield.

Cycloadditions with benzoquinone and naphthoquinone under thermal conditions provided the adducts **32** and **33**, respectively, whereas under photolytic conditions[41] a hetero [4 + 2] mode of cycloaddition furnished **34**. Both quinones reacted from the less hindered face and in an endo manner. The structure of **32** was elucidated by means of the NOE: irradiation of H1 enhanced the signals of H3, H4, and H5, which is possible only if the product has the endo configuration. The structure of adduct **33** was confirmed by NOE. The stereochemistry of the photolytic adduct **34** was shown by heteronuclear multibond correlation technique (HMBC), which showed that the spirocyclic carbon of the quinone adduct, marked with an asterisk, is no more than three bonds away from H4. This feature is possible in **34** but not in its regioisomer.

Addition of nitrile oxide (generated from nitroethane)[42] in a [3 + 2] dipolar cycloaddition gave a high yield of isoxazole **35**, whose acquision opens a new area of synthesis of homochiral heterocyclic compounds.[2c] Exposure of **6b** to tropone furnished

(32) We are grateful to Professor Noritaka Chida of Keio University for supplying us with detailed experimental procedures for this transformation and the ^1H NMR spectrum of lycoricidine.

(33) (a) Grigg, R.; Santhamukar, V.; Sridharan, V.; Thornton-Pett, M.; Bridge, A. W. *Tetrahedron* **1993**, *49*, 5177. (b) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 7471.

(34) Lopes, R. S. C.; Lopes, C. C.; Heathcock, C. H. *Tetrahedron Lett.* **1992**, *33*, 6775; 35. Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.

(35) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.

(36) Hudlicky, T.; Königsberger, K.; Tian, X. *J. Org. Chem.*, in press. A full study of ring-opening tendencies of aza- and oxabicyclo[4.1.0]heptanes is in progress.

(37) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.

(38) Review of literature indicates that whereas the chemistry of vinyloxiranes is well understood, the interactions of vinylaziradines with nucleophiles have been limited to the iodine-catalyzed rearrangements to pyrrolines. For a comprehensive review of the chemistry of vinylcyclopropanes, vinyloxiranes, and vinylaziridines, see: Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 8.1.

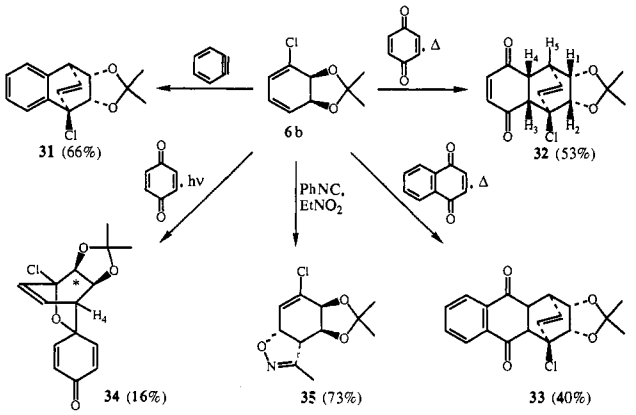
(39) Conditions adapted from: Eis, M. J.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1153.

(40) Banwell, M., private communication.

(41) (a) Beltrop, J.; Hesp, B. *J. Chem. Soc.* **1965**, 5182. (b) Burger, U.; Lottaz, P.-A.; Millissan, P.; Bernardinelli, G. *Helv. Chim. Acta* **1994**, in press.

(42) (a) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339. (b) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Guarneri, M.; Simoni, D.; Gandolfi, C. *J. Org. Chem.* **1981**, *46*, 4518.

Scheme 3



a 16% yield of adduct **36**,[43] which was dehalogenated to **37**, foundidentical to the compound previously prepared by Roberts.[23b]

These results are completely consistent with the theoretical analysis of the polarized diene unit in diols or their acetonides. The formation of **35** is expected to proceed with the regiochemistry as shown, based on both the electron content of the C4–C5 olefin relative to the chloro olefin at C6–C1 and the polarization of the C4–C5 bond, which establishes at C5 an incipient allylic cation. To our knowledge, the quinone addition and the [3 + 2] cycloaddition are the first cases of cycloadditions of such species with the homochiral dienediols. Clearly these results have enormous significance for future endeavors in the area of anthracyclin-type antibiotics or the synthesis of heterocyclic equivalents of cyclitols. In **35**, a carbon residue has been substituted at C4, and this is significant in terms of producing functionalized diol derivatives that may not be available from dioxygenase-mediated oxidation of arenes. These results bode well for application of these cycloadditions to pursuits in the area of polycyclic oxygenated compounds, and these will be reported in due course.

Conclusion

A concise demonstration of cycloaddition potential has been made for homochiral polarized 1,3-cyclohexadiene-*cis*-diols derived from all four halobenzenes via biocatalysis with bacterial dioxygenase from *Pseudomonas putida* 39D. The results are consistent with predictions based on calculated HOMO coefficients as well as on calculated charge densities of the polarized halodienes. Applications of nitrosyl cycloaddition to conduramine and lycoricidine synthesis have emerged as a result of the detailed study.

A new area of application of cycloaddition with quinones, tropone, and 1,3-dipoles has been discovered. A novel approach to pancratistatin via nucleophilic opening of homochiral vinylaziridine will lead to the delivery of this alkaloid in a brief manner. This article concludes the three-part presentation of diverse methodology based on the use of homochiral dienediols derived from halogenated aromatics. The synthetic applications expressed in the carbohydrate area are brief and provide new environmentally sound protocols for the synthesis of oxygenated compounds.

(43) Tian, X.; Hudlicky, T., unpublished observations. Dimerization of **6b** to **15** accounted for the rest of the mass balance. The dehalogenated structure **37** (prepared in 81% yield by treatment with AIBN and Bu_3SnH in toluene) was found intentical to the adduct prepared from *meso*-cyclohexadienediol acetonide by Roberts (ref 23b).

Experimental Section

General. All nonhydrolytic reactions were conducted in oven-dried or flame-dried glassware under atmospheres of dry argon. All solvents were reagent grade. Anhydrous solvents were dried immediately before use. Ether and THF were distilled from sodium benzophenone ketyl. Methylene chloride, 1,2-dichloroethane, diisopropylethylamine, pyridine, hexamethyldisilazane, chlorotrimethylsilane, triethylamine, dimethylformamide, and *tert*-butyldimethylsilyl chloride were distilled from CaH_2.

Analytical TLC was performed on silica gel Merck kieselgel 60 F_{254} (0.25-mm thickness) plates. The plates were visualized by immersion in a *p*-anisaldehyde solution or phosphomolybdic acid solution (EtOH 95%) followed by warming on a hot plate. Flash chromatography was carried out on Merck kieselgel 60 silica gel (230–400 mesh). Mass spectra were recorded on a Varian MAT-112 instrument (low resolution) or on a double-focusing VG 7070 E-HF instrument (exact mass). Infrared spectra were recorded on Perkin-Elmer 283B or 710B instruments. NMR spectra were recorded on a Bruker WP-270 instrument. Proton chemical shifts are reported in parts per million (ppm) relative to TMS, as are carbon chemical shifts. Rotations were recorded on a Perkin-Elmer 241 digital polarimeter. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., P.O. Box 2288, Norcross, GA 30091.

(1*S*,2*S*,3*S*,4*R*)-5-(Ethoxycarbonyl)-1-fluoro-2,3-*O*-isopropylidenebicyclo-[2.2.2]octa-5,7-diene-2,3-diol (19a) and (1*S*,2*S*,3*S*,4*R*)-1-Fluoro-6-(ethoxycarbonyl)-2,3-*O*-isopropylidenebicyclo[2.2.2]octa-5,7-diene-2,3-diol (20a). To fluorobenzenediol acetonide **6a** (237.5 mg, 1.397 mmol) in benzene (5 mL) was added ethyl propiolate (0.283 mL, 2.79 mmol), and the solution was heated to reflux under argon for 48 h. Solvent was evaporated, and the mixture was chromatographed in silica gel (hexane/ethyl acetate, 9:1). Two cycloadducts were obtained: 119.6 mg (0.45 mmol, 32%) of the less polar Diels–Alder adduct **19a** as an oil followed by 172 mg (46%) of the more polar adduct **20a**.

19a: R_f 0.41 (hexane/EtOAc, 4:1); IR (KBr) ν 3020, 2983, 1712, 1374, 1216, 1051 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (1H, d, J = 11 Hz), 6.43 (1H, dd, J = 9, 9 Hz), 6.30 (1H, m), 4.43 (1H, m), 4.35 (2H, m), 4.20 (2H, q, J = 7 Hz), 1.37 (3H, s), 1.29 (3H, s), 1.29 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 163.5 (CO), 143.9 (CH), 135.5 (C), 132.0 (CH), 130.1 (C), 115.0 (C), 80.0 (CH), 79.8 (CH), 78.2 (CH), 61.1 (CH_2), 41.5 (CH), 25.8 (CH_3), 25.6 (CH_3), 14.2 (CH_3); MS (CI, 70 eV) *m/z* (relative intensity) 269 (M^+, 60), 211 (20), 169 (95), 100 (100). Anal. Calcd for $C_{14}H_{17}O_4F$: C, 62.68; H, 6.39. Found: C, 62.75; H, 6.41.

20a: R_f 0.25 (hexane/ethyl acetate, 4:1); mp 64–65.5 °C; IR (KBr) ν 3077, 2985, 1724, 1370, 1245, 1104 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (1H, dd, J = 6.2, 6.2 Hz), 6.50 (1H, m), 6.24 (1H, m), 4.51 (1H, ddd, J = 7, 7, 1.5 Hz), 4.35 (1H, m), 4.23 (2H, q, J = 7.2 Hz), 3.91 (1H, dddd, J = 3.5, 3.5, 3.5, 1.6 Hz), 1.37 (3H, s), 1.30 (3H, s), 1.30 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 162.8 (CO), 140.1 (CH), 139.5 (C, d, J = 21 Hz), 133.3 (CH, d, J = 21 Hz), 128.7 (CH, J = 12.6 Hz), 115.1 (C), 80.4 (CH, d, J = 17 Hz), 78.2 (CH), 60.8 (CH_2), 42.2 (CH), 25.8 (CH_3), 25.7 (CH_3), 14.2 (CH_3); MS (CI, 70 eV) *m/z* (relative intensity) 269 (M^+, 100), 211 (15), 191 (20), 169 (60). Anal. Calcd for $C_{14}H_{17}O_4F$: C, 62.68; H, 6.39. Found: C, 62.68; H, 6.34.

(1*S*,2*S*,3*S*,4*R*)-1-Chloro-5-(ethoxycarbonyl)-2,3-*O*-isopropylidenebicyclo[2.2.2]octa-5,7-diene-2,3-diol (19b) and (1*S*,2*S*,3*S*,4*R*)-1-Chloro-6-(ethoxycarbonyl)-2,3-*O*-isopropylidenebicyclo[2.2.2]octa-5,7-diene-2,3-diol (20b). To chlorobenzenediol acetonide **6b** (580 mg, 3.126 mmol) in benzene (5 mL) was added ethyl propiolate (0.613 mL, 6.25 mmol), and the solution was heated at reflux under argon for 48 h. Solvent was evaporated, and the mixture was chromatographed on silica gel (hexane/ethyl acetate, 9:1). Two cycloadducts were obtained: 195 mg (0.685 mmol, 22%) of the less polar Diels–Alder adduct **20b** and 155 mg of **19b** as oils (40% combined yield).

19b: R_f 0.42 (hexane/ethyl acetate, 4:1); $[\alpha]^{20}_D$ +49.6° (*c* 1.4, $CHCl_3$); IR (KBr) ν 3019, 2983, 1713, 1630, 1591, 1374, 1246, 1064 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (1H, s), 6.37 (1H, m), 6.29 (1H, d, J = 7.5 Hz), 4.35 (3H, m), 4.19 (2H, q, J = 5.6 Hz), 1.37 (3H, s), 1.30 (3H, t, J = 5.6 Hz), 1.29 (3H, s); ^{13}C NMR ($CDCl_3$) δ 163.2 (CO), 146.8 (CH), 137.0 (C), 135.0 (CH), 131.5 (CH), 114.3 (C), 83.9 (CH), 79.1 (CH), 69.8 (C), 61.0 (CH_2), 41.1 (CH), 25.7 (CH_3), 25.5 (CH_3), 14.1 (CH_3); MS (CI, 70 eV) *m/z* (relative intensity) 285 (M + 1, 25), 227 (23), 185 (100), 151(30), 100 (95). Anal. Calcd for $C_{14}H_{17}O_4Cl$: C, 59.05; H, 6.02. Found: C, 59.00; H, 6.00.

20b: R_f 0.24 (hexane/ethyl acetate, 4:1); mp 78–79 °C; $[\alpha]^{20}_D$ +42.4° (*c* 0.8, $CHCl_3$); IR (KBr) ν 3019, 2984, 2936, 1722, 1630, 1588, 1374, 1215, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91 (1H, d, J = 6.5 Hz), 6.36

(1H, m), 6.30 (1H, d, J = 7.5 Hz), 4.40 (2H, m), 4.23 (2H, q, J = 7 Hz), 3.92 (1H, m), 1.39 (3H, s), 1.31 (3H, t, J = 7 Hz), 1.31 (3H, s); ^{13}C NMR ($CDCl_3$) δ 163.8 (CO), 140.2 (C), 139.3 (CH), 136.7 (CH), 130.5 (CH), 114.3 (C), 83.9 (CH), 78.9 (CH), 68.4 (C), 60.9 (CH_2), 41.6 (CH), 25.7(CH_3), 25.5 (CH_3), 14.0 (CH_3); MS (CI, 70 eV) m/z (relative intensity) 285 (M + 1, 95), 227 (20), 185 (95), 100 (100). Anal. Calcd for $C_{14}H_{17}O_4Cl$: C, 59.05; H, 6.02. Found: C, 58.95; H, 6.01.

(1*S*,2*S*,3*S*,4*R*)-1-Bromo-5-(ethoxycarbonyl)-2,3-*O*-isopropylidenebicyclo[2.2.2]octa-5,7-diene-2,3-diol (19c) and (1*S*,2*S*,3*S*,4*R*)-1-Bromo-6-(ethoxycarbonyl)-2,3-*O*-isopropylidenebicyclo[2.2.2]octa-5,7-diene-2,3-diol (20c). To bromobenzenediol acetonide **6c** (1.05 g, 4.54 mmol) in benzene (10 mL) was added ethyl propiolate (0.92 mL, 9 mmol), and the solution was heated at reflux under argon for 24 h. Solvent was evaporated, and the mixture was chromatographed on silica gel (hexane/ethyl acetate, 9:1) to give Diels–Alder adducts **19c** (318 mg, 21%) and **20c** (591 mg, 40%).

19c: R_f 0.41 (hexane/EtOAc, 4:1); $[\alpha]^{20}_D$ +46.7° (c 1.0, $CHCl_3$); IR (KBr) ν 3078, 2981, 1716, 1372, 1243, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.23 (1H, d, J = 1 Hz), 6.38 (1H, d, J = 7, 5 Hz), 6.32 (1H, m), 4.35 (3H, m), 4.22 (2H, q, J = 7 Hz), 1.39 (3H, s), 1.30 (3H, s), 1.29 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 163.3 (CO), 147.6 (CH), 137.6 (C), 136.1 (CH), 131.9 (CH), 114.2 (C), 84.7 (CH), 79.4 (CH), 61.1 (CH_2), 60.4 (C), 40.9 (CH), 25.8 (CH_3), 25.6 (CH_3), 14.1 (CH_3); MS (CI, 70 eV) m/z (relative intensity) 329 (M^+, 28), 151 (95), 100 (100). Anal. Calcd for $C_{14}H_{17}O_4Br$: C, 51.08; H, 5.20. Found: C, 50.99; H, 5.16.

20c: R_f 0.32 (hexane/EtOAc, 4:1); mp 87 °C ; $[\alpha]^{20}_D$ +102° (c 1.4, $CHCl_3$); IR (KBr) ν 3072, 2983, 1717, 1238, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.83 (1H, d, J = 7 Hz), 6.44 (1H, dt, J = 7, 1 Hz), 6.22 (1H, td, J = 7, 1 Hz), 4.43 (1H, dd, J = 7, 1 Hz), 4.32 (1H, ddd, J = 7, 3.5, 1 Hz), 4.22 (2H, q, J = 7 Hz), 3.88 (1H, m), 1.37 (3H, s), 1.29 (2CH_3, st, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 164.4 (CO), 140.4 (C), 138.8 (CH), 137.8 (CH), 131.0 (CH), 114.1 (C), 84.5 (CH), 79.0 (CH), 61.1 (CH_2), 58.9 (C), 41.5 (CH), 25.8 (CH_3), 25.5 (CH_3), 14.1 (CH_3); MS (EI, 70 eV) m/z (relative intensity) 313 (M^+ – 16, 1.5), 100 (100), 85 (95). Anal. Calcd for $C_{14}H_{12}O_4Br$: C, 51.08; H, 5.20. Found: C, 51.20; H, 5.24.

(1*S*,2*S*,3*S*,4*R*)-5-(Ethoxycarbonyl)-1-iodo-2,3-*O*-isopropylidenebicyclo-[2.2.2]octa-5,7-diene-2,3-diol (19d) and (1*S*,2*S*,3*S*,4*R*)-5-(Ethoxycarbonyl)-1-iodo-2,3-*O*-isopropylidenebicyclo[2.2.2]octa-5,7-diene-2,3-diol (20d). Iodobenzenediol acetonide **6d** (263 mg, 0.946 mmol) was diluted in benzene (10 mL). Ethyl propiolate (0.192 mL, 1.892 mmol) was added and the solution was heated to reflux under argon for 24 h. Solvent was evaporated, and the mixture was chromatographed in silica gel (hexane/ethyl acetate, 9:1). Diels–Alder adducts **19d** (73.2 mg, 21%) and **20d** (120 mg, 33%) were obtained. Also isolated was the Diels–Alder dimer **15** (90 mg).

19d: R_f 0.47 (hexane/ethyl acetate, 4:1); $[\alpha]^{20}_D$ +45.5° (c 1.3 $CHCl_3$); IR (KBr) ν 3073, 2981, 1716, 1623, 1584, 1372, 1243, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (1H, d, J = 1.6 Hz), 6.47 (1H, dt, J = 7.4, 1.3 Hz), 6.18 (1H, td, J = 6, 1.3 Hz), 4.43 (1H, dd, J = 6.7, 1 Hz), 4.30 (2H, m), 4.21 (2H, q, J = 7 Hz), 1.38 (3H, s), 1.30 (3H, s), 1.30 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 163.1 (CO), 150.2 (CH), 138.7 (CH), 138.1 (C), 132.4 (CH), 113.6 (C), 86.3 (CH), 79.0 (CH), 61.1 (CH_2), 40.1 (CH), 36.0 (C), 25.8 (CH_3), 25.5 (CH_3), 14.1 (CH_3); MS (CI, 70 eV) m/z (relative intensity) 377 (M + 1, 10), 277 (50), 100 (100). Anal. Calcd for $C_{14}H_{17}O_4I$: C, 44.70; H, 4.55. Found: C, 44.80; H, 4.56.

20d: R_f 0.27 (hexane/ethyl acetate, 4:1); $[\alpha]^{20}_D$ +115° (c 1.1, $CHCl_3$); mp 74–76 °C; IR (KBr) ν 3054, 2984, 1716, 1623, 1378, 1304, 1235, 1089 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.84 (1H, d, J = 6.5 Hz), 6.64 (1H, d, J = 7.5 Hz), 6.09 (1H, dd, J = 7.6, 6.0 Hz), 4.45 (1H, d, J = 7.0 Hz), 4.30 (1H, dd, J = 7.0, 5.4 Hz), 4.21 (2H, q, J = 7.1 Hz), 3.90 (1H, m), 1.40 (3H, s), 1.32 (3H, t, J = 7.1 Hz), 1.31 (3H, s); ^{13}C NMR ($CDCl_3$) δ 164.9 (CO), 141.3 (CH), 141.1 (C), 138.5 (CH), 131.6 (CH), 113.6 (C), 86.1 (CH), 78.9 (CH), 61.2 (CH_2), 41.2 (CH), 35.2 (CH), 25.9 (CH_3), 25.6 (CH_3), 14.2 (CH_3); MS (CI, 70 eV) m/z (relative intensity) 377 (M + 1, 30), 277 (22), 191 (40), 151 (10), 100 (100). Anal. Calcd for $C_{14}H_{17}O_4I$: C, 44.70; H, 4.55. Found: C, 44.97; H, 4.58.

3-(Benzyloxycarbonyl)-1-fluoro-5,6-*O*-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (21a). Benzylhydroxamic acid (229 mg) was added slowly to a solution of protected fluorodiol **6a** (212 mg) and Bu_4NIO_4 (594 mg) in CH_2Cl_2 (30 mL) in an ice bath. After 1 h, the solution was washed with 20% sodium thiosulfate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The Diels–Alder adduct was purified by column chromatography (silica gel, 7.5:2.5, hexane/ethyl acetate) to give 80 mg (24% yield) of the product: R_f 0.24 (hexane/ethyl acetate, 8:2); IR (KBr) ν 3032, 2992, 1759, 1720, 1384, 1269, 1222 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5H), 6.47 (m, 1H), 6.37 (tt, J = 9, 1.5 Hz, 1H), 5.23 (d, J = 19 Hz, 1H), 5.22 (d, J = 19 Hz, 1H), 5.06 (m, 1H), 4.67 (m, 1H), 4.46 (td, J = 9, 1.5, 1H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.7 (CO), 135.4 (C), 132.0 (CH), 129.2 (CH), 129.0 (CH), 128.8 (2CH), 128.1 (2CH), 112.3 (C), 76.8 (C), 74.4 (CH), 69.7 (CH), 68.6 (CH_2), 54.4 (CH), 25.6 (CH_3), 25.4 (CH_3); MS (CI, 70 eV) m/z (relative intensity) 336 (M + 1, 10), 292 (100). Anal. Calcd for $C_{17}H_{18}NO_5F$: C, 60.89; H, 5.41; N, 4.18. Found: C, 61.54; H, 5.30; N, 3.86.

3-(Benzyloxycarbonyl)-1-chloro-5,6-*O*-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (21b). Benzylhydroxamic acid (391 mg) was added slowly to a solution of protected chlorodiol **6b** (397 mg) and Bu_4NIO_4 (102 mg) in CH_2Cl_2 (7 mL) cooled in an ice bath. After 1 h, the solution was washed with 20% sodium thiosulfate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The Diels–Alder adduct was purified by column chromatography (silica gel, 7.5:2.5, hexane/ethyl acetate) to give 405 mg (54% yield) of the product: R_f 0.24 (hexane/ethyl acetate, 8:2); $[\alpha]^{20}_D$ +21.4 (c 2.7, $CHCl_3$); IR (KBr) ν 3067, 3034, 2991, 2937, 1755, 1610, 1384, 1269, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 5H), 6.45 (dd, J = 8.5, 5.6 Hz, 1H), 6.37 (d, J = 8.2 Hz, 1H), 5.20 (d, J = 19.2 Hz, 1H), 5.16 (d, J = 19.2 Hz, 1H), 5.07 (m, 1H), 4.65 (dd, J = 7, 4 Hz, 1H), 4.51 (d, J = 7, 1H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.8 (CO), 135.4 (C), 132.9 (2CH), 131.7 (CH), 128.6 (2CH), 128.4 (CH), 128.0 (CH), 111.8 (C), 95.0 (C), 80.5 (CH), 74.3 (CH), 68.6 (CH_2), 53.7 (CH), 25.6 (CH_3), 25.4 (CH_3); MS (CI, 70 eV) m/z (relative intensity) 352 (M^+, 5), 308 (25), 91 (100). Anal. Calcd for $C_{17}H_{18}NO_5Cl$: C, 58.04; H, 5.16. Found: C, 58.14; H, 5.18.

3-(Benzyloxycarbonyl)-1-bromo-5,6-*O*-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (21c). Benzylhydroxamic acid (385 mg) was added slowly to a solution of protected bromodiol **6c** (266.5 mg) and Bu_4NIO_4 (500 mg) in CH_2Cl_2 (10 mL) cooled in an ice bath. After 1 h, the solution was washed with 20% sodium thiosulfate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The Diels–Alder adduct was purified by column chromatography (silica gel, 8:2, hexane/ethyl acetate) to give 330 mg (74% yield) of **21c**: R_f 0.48 (hexane/ethyl acetate, 7:3); $[\alpha]^{20}_D$ +16.1° (c 9.5, $CHCl_3$); mp 69–70 °C; IR (KBr) ν 3067, 2992, 1755, 1714, 1607, 1269, 1212 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5H), 6.49 (dd, J = 8.5, 1.4 Hz, 1H), 6.36 (dd, J = 8.6, 5.6 Hz, 1H), 5.22 (d, J = 12.3 Hz, 1H), 5.15 (d, J = 12.3 Hz, 1H), 5.05 (m, 1H), 4.61 (m, 2H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.8 (CO), 135.4 (C), 134.1 (2CH), 131.5 (CH), 128.5 (2CH), 128.4 (CH), 128.0 (CH), 111.5 (C), 87.5 (C), 81.4 (CH), 74.3 (CH), 68.5 (CH_2), 53.3 (CH), 25.7 (CH_3), 25.4 (CH_3); MS (EI, 70 eV) m/z (relative intensity) 395 (M^+, 1), 100 (10), 91 (100). Anal. Calcd for $C_{17}H_{18}NO_5Br$: C, 51.53; H, 4.58. Found: C, 51.40; H, 4.58.

3-Benzoyl-1-bromo-5,6-*O*-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (21d). Benzohydroxamic acid (421 mg, 3.07 mmol) was added slowly to a solution of protected bromodiol **6c** (355 mg, 1.54 mmol) and Bu_4NIO_4 (533 mg, 0.8 equiv) in CH_2Cl_2 (5 mL) cooled in an ice bath. After 2 h, the solution was washed with 20% sodium thiosulfate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The Diels–Alder adduct was purified by column chromatography (silica gel, 9:1, hexane/ethyl acetate) to yield 350 mg (1.07 mmol, 70% yield) of **21d**: R_f 0.41 (hexane/ethyl acetate, 7:3); mp 150–155 °C; $[\alpha]^{20}_D$ +52° (c 1.0, $CHCl_3$); IR (KBr) ν 3344, 3074, 2984, 1660, 1605, 1271 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, m), 7.45 (3H, m), 6.49 (2H, m), 5.44 (1H, m), 4.72 (2H, m), 1.38 (3H, s), 1.36 (3H, s); ^{13}C NMR ($CDCl_3$) δ 172.2 (C), 133.9 (CH), 132.7 (CH), 132.4 (C), 131.9 (CH), 129.3 (2CH), 128.1 (2CH), 111.5 (C), 88.1 (C), 81.5 (CH), 74.1 (CH), 51.2 (CH), 25.6 (CH_3), 25.3 (CH_3); MS (EI, 70 eV) m/z (relative intensity) 366 (M^+, 6), 228 (11), 105 (98), 77 (100). Anal. Calcd for $C_{16}H_{16}NO_4Br$: C, 52.48; H, 4.40. Found: C, 52.53; H, 4.44.

3-Acetyl-1-bromo-5,6-*O*-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (21e). *N*-Acetohydroxamic acid (170 mg, 2.27 mmol) was added slowly to a solution of protected bromodiol **6c** (525 mg, 2.273 mmol) and Bu_4NIO_4 (492 mg, 1.136 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath. After 1 h, the solution was washed with 20% sodium thiosulfate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The Diels–Alder adduct was purified by column chromatography (silica gel, 7.5:2.5, hexane/ethyl acetate) to yield **21e** (351 mg, 1.15 mmol, 51% yield): R_f 0.34 (hexane/ethyl acetate, 4:1); mp 99–102

°C; $[\alpha]^{20}_D$ −13.7° (*c* 4.3, $CHCl_3$); IR (KBr) *ν* 3076, 1657, 1606, 1384 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 6.43 (1H, m), 5.41 (1H, m), 4.60 (1H, dd, *J* = 7.0, 0.6 Hz), 4.53 (1H, ddd, *J* = 7.0, 4.0, 0.7 Hz), 2.04 (3H, s), 1.34 (1H, s), 1.31 (3H, s); ^{13}C NMR ($CDCl_3$) *δ* 174.2 (C), 133.8 (CH), 132.5 (2CH), 111.5 (C), 88.2 (C), 81.4 (CH), 74.1 (CH), 49.8 (CH), 25.6 (CH_3), 25.3 (CH_3), 21.7 (CH_3); MS (EI, 70 eV) *m/z* (relative intensity) 304 (M^+, 10), 288 (65), 156 (95), 124 (100), 94 (85). Anal. Calcd for $C_{11}H_{14}NO_4Br$: C, 43.44; H, 4.64; N: 4.61. Found: C, 43.51; H, 4.64; N, 4.51.

3-(*o*-Bromopiperonyl)-1-bromo-5,6-*O*-isopropylidene-2-oxa-3-azabicyclo-[2.2.2]oct-7-ene-5,6-diol (21f). (Bromopiperonyl)hydroxamic acid[44] (492 mg, 2 equiv) was added slowly to a solution of protected bromodiol **6c**[16,45] (219 mg) and Bu_4NIO_4 (328 mg, 0.8 equiv) in CH_2Cl_2 (6 mL) cooled in an ice bath. After 2 h, the solution was washed with 20% sodium thiosulfate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The Diels–Alder adduct was purified by column chromatography (silica gel, 4:1, hexane/ethyl acetate) to give **21f** (366 mg, 80% yield): R_f 0.43 (hexane/ethyl acetate, 7:3); mp 75 °C; IR (KBr) 3018, 1656, 1480, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.33 (s, 5H), 6.49 (dd, *J* = 8.5, 1.4 Hz, 1H), 6.36 (dd, *J* = 8.6, 5.6 Hz, 1H), 5.22 (d, J = 12.3 Hz, 1H), 5.15 (d, *J* = 12.3 Hz, 1H), 5.05 (m, 1H), 4.61 (m, 2H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 149.6, 147.2, 134.4, 131.1, 128.7, 113.1, 111.6, 111.0, 108.5, 102.2, 102.0, 87.9, 81.1, 77.3, 73.9, 73.6, 25.5, 25.4; MS (EI, 70 eV) *m/z* (relative intensity) 395 (M^+, 1), 100 (10), 91 (100). Anal. Calcd for $C_{17}H_{15}NO_6Br_2$: C, 41.75; H, 3.09. Found: C, 41.85; H, 3.12.

(1*S*,2*R*,3*S*,6*R*)-6-(*N*-(*o*-Bromopiperonyl)amino)-1,2-*O*-isopropylidenecyclohex-4-ene-1,2,3-triol (22b). To a stirred solution of the Diels–Alder adduct **21f** (221 mg, 0.056 mmol) in aqueous tetrahydrofuran (THF:H_2O, 10:1, 11 mL) cooled to 0 °C was added aluminum amalgam (prepared from 105 mg, 3.9 mmol, 7 equiv of Reynolds heavy-duty aluminum foil),[30] and stirring was continued at 0 °C. After 6 h, the reaction was complete. The reaction mixture was diluted with 30 mL of THF, stirred for 10 min, and then filtered through Celite. The filtrate was diluted with toluene and concentrated under reduced pressure to afford the hydroxy carbamate **22b** (161 mg, 0.51 mmol, 91%). An analytical sample was obtained by column chromatography (silica gel, hexane/ethyl acetate, 1:1), and recrystallized from CH_2Cl_2/hexane: R_f 0.32 (hexane/ethyl acetate, 1:1); mp 113–114 °C; $[\alpha]^{20}_D$ −41° (*c* 8, $CHCl_3$); IR (KBr) *ν* 3338, 2989, 1702, 1522, 1217, 1064 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.37 (m, 5H), 5.96 (m, 1H), 5.83 (dd, *J* = 9.8, 2.2 Hz, 1H), 5.31 (bs, 1H), 5.13 (d, *J* = 2.8 Hz, 1H), 4.23 (m, 4H), 4.18 (m, 1H), 2.64 (bs, 1H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 155.9 (CO), 136.3 (C), 131.1 (CH), 129.8 (CH), 128.5 (2CH), 109.2 (C), 79.2 (C), 77.0 (CH), 69.1 (CH), 67.0 (CH_2), 51.3 (CH), 27.0 (CH_3), 24.7 (CH_3); MS (Cl, 70 eV) *m/z* (relative intensity) 320 (M + 1, 20), 262 (30), 212 (100), 91 (50). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63. Found: C, 63.99; H, 6.64.

(1*S*,2*R*,3*S*,6*R*)-6-((Benzyloxycarbonyl)amino)-1,2-*O*-isopropylidene-3-((isopropyldimethylsilyl)oxy)cyclohex-4-ene-1,2-diol (22c). Imidazole (293 mg, 4.31 mmol) was added to a solution of alcohol **22a**[2a,21] (625 mg, 1.96 mmol) in 20 mL of dry CH_2Cl_2. The solution was cooled to 0 °C. Isopropyldimethylsilane chloride was added (335 mg, 2.15 mmol). After 10 h the reaction was complete. The solution was filtered, washed with water (15 mL) and brine (15 mL), and dried with sodium sulfate. Solvent was removed after filtration to yield 803 mg (1.91 mmol, 98%) of solid **22c**. An analytical sample was purified by column chromatography (silica gel, hexane/ethyl acetate, 4:1): R_f 0.34 (hexane/ethyl acetate, 4:1); mp 71–72 °C; $[\alpha]^{20}_D$ −14° (*c* 1.0, $CHCl_3$); IR (KBr) 3332, 3052, 2941, 1692, 1539, 1260, 1112, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.34 (m, 5H), 5.99 (m, 2H), 5.11 (m, 2H), 5.51 (bs, 1H), 4.25 (m 3H), 4.20 (m, 1H), 4.18 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 0.95 (m, 6H), 0.85 (m, 1H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 155.8 (CO), 136.7 (C), 132.5 (CH), 130.2 (CH), 128.4 (2CH), 127.9 (2CH), 108.5 (C), 79.0 (CH), 77.4 (CH), 77.2 (CH), 67.8 (CH), 66.7 (CH_2), 49.1 (CH), 26.6 (CH_3), 24.6 (CH_3), 16.8 (CH_3), 14.6 (CH_3), −3.9 ($2CH_3$); MS (CI, 70 eV) *m/z* (relative intensity) 420 (M + 1, 40), 302 (100), 91 (70). Anal. Calcd for $C_{22}H_{33}NSiO_5$: C, 62.98; H, 7.93, N, 3.34. Found: C, 62.79; H, 7.96; N, 3.29.

(44) This compound was prepared from the corresponding acid by treatment with thionyl chloride. The acid is prepared by bromination of piperonal (Becker, D.; Hughes, L. R.; Raphael, *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674 and either $KMnO_4$ or Ag_2O oxidation (Dallacker, F. *Liebigs Ann. Chem.* **1960**, *633*, 14).

(45) For a laboratory scale synthesis of this compound, see: Hudlicky, T.; Boros, E. E.; Boros, C. H. *Synthesis* **1992**, 174.

(1*S*,2*R*,3*S*,6*R*)-6-(*N*-(Benzyloxycarbonyl)-N-(*o*-bromopiperonyl)-amino)-1,2-*O*-isopropylidene-3-((isopropyldimethylsilyl)oxy)cyclohex-4-ene-1,2-diol (23). To a solution of carbamate **22c** (200 mg, 0.476 mmol) in 4 mLof freshly distilled THF at −78 °C was added *n*-butyllithium (0.281 mL, 2.54 M). A solution of *o*-bromopiperonic acid chloride (266 mg, 0.953 mmol) in 4 mL of THF was added. The stirred reaction mixture was allowed to warm to 0 °C; after 1 h aqueous $KHCO_3$ was added. After 1 h, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate. Combined organic layers were washed with brine and dried with Na_2SO_4. Evaporation of the solvent followed by column chromatography (silica gel, hexane/ethyl acetate, 8:2) yielded 237 mg (0.367 mmol, 77% yield) of **23**: R_f 0.33 (hexane/ethyl acetate, 4:1); $[\alpha]^{20}_D$ −28.9° (*c* 0.9 $CHCl_3$); IR (neat) *ν* 2953, 1740, 1679, 1620, 1481, 1244, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.3 (3H, m), 7.12 (2H, m), 6.78 (1H, s), 6.75 (1H, s), 5.94 (2H, s), 5.69 (2H, s), 5.20 (1H, dd), 5.07 (1H, d, *J* = 12 Hz), 5.02 (1H, d, *J* = 12 Hz), 4.63 (1H, dd, *J* = 7.0 Hz), 4.20 (1H, dd, *J* = 5.5, 2.2 Hz), 4.10 (1H, dd, *J* = 7.1, 5.5 Hz), 1.47 (3H, s), 1.33 (3H, s), 0.95 (7H, m), 0.2 (3H, s), 0.1 (3H, s); ^{13}C NMR *δ* 169.6 (CO), 153.5 (CH), 149.2 (C), 147.2 (C), 134.1 (C), 132.4 (C), 131.3 (2CH), 128.8 (CH), 128.6 (2CH), 128.3 (2CH), 126.5 (CH), 112.8 (CH), 110.2 (CH), 108.4 (C), 102.0 (CH_2), 88.7 (CH), 80.2 (CH), 75.1 (CH), 71.3 (CH), 69.3 (CH_2), 57.0 (CH), 27.5 (CH_3), 25.5 (CH_3), 16.9 (CH_3), 14.7 (CH_3), −3.6 (CH_3), −3.9 (CH_3); MS (CI, 70 eV) *m/z* (relative intensity) 648 (M + 1, 2), 590 (10), 530 (100). Anal. Calcd for $C_{30}H_{36}O_8NSiBr$: C, 55.73; H, 5.61; N, 2.17. Found: C, 55.48; H, 5.60; N, 2.13.

(2*S*,3*R*,4*S*,4a*R*)-5-(Benzyloxycarbonyl)-2-((isopropyldimethylsilyl)-oxy)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-2,3,4,4a-tetrahydro-6-phenanthridone (24). A mixture of bromo olefin **23** (180 mg, 0.278 mmol), $Pd(OAc)_2$ (12.5 mg, 0.055 mmol), 1,2-bis(diphenylphosphino)ethane (44.4 mg, 0.11 mmol), and Tl(OAc) (144 mg, 0.556 mmol) in anisole (6 mL) was heated at 135 °C for 7 h. The reaction mixture was diluted with EtOAc, and the insoluble material was removed by filtration. The filtrate and washings (EtOAc) were combined and concentrated. The resulting residue was chromatographed on silica gel (hexane/ethyl acetate, 4:1) to give 42.6 mg (0.075 mmol, 27%) of cyclized compound **24**: R_f 0.22 (hexane/ethyl acetate, 4:1); $[\alpha]^{20}_D$ +20° (*c* 0.9, $CHCl_3$); IR (neat) *ν* 3066, 2940, 1758, 1670, 1479, 1251, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.61 (1H, s), 7.48 (2H, m), 7.38 (3H, m), 7.01 (1H, s), 6.24 (1H, t, *J* = 3 Hz), 6.04 (2H, s), 5.47 (1H, d, *J* = 12 Hz), 5.25 (1H, d, *J* = 12 Hz), 4.89 (1H, dd, *J* = 8, 3 Hz), 4.40 (1H, m), 4.18 (2H, m), 1.40 (3H, s), 1.26 (3H, s), 1.01 (7H, t, m), 0.14 (6H, t, s); ^{13}C NMR ($CDCl_3$) *δ* 161.0 (CO), 155.0 (CO), 152.5 (C), 148.8 (C), 135.0 (C), 128.6 (C), 128.5 (2CH), 128.2 (3CH), 127.6 (2CH), 127.1 (CH), 121.0 (CH), 111.7 (C), 108.2 (CH), 102.0 (CH_2), 101.0 (CH_2), 80.1 (CH), 79.9 (CH), 73.5 (CH), 69.4 (CH), 58.7 (CH), 26.9 (CH_3), 25.0 (CH_3), 16.9 (CH_3), 14.7 (CH_3), −3.6 (CH_3), −3.8 (CH_3), −3.4 (CH); MS (CI, 70 eV) *m/z* (relative intensity) 566 (M + 1, 30), 522 (50), 432 (70), 256 (70), 91 (100). Anal. Calcd for $C_{30}H_{35}O_8NSi$: C, 63.70; H, 6.24; N, 2.48. Found: C, 63.56; H, 6.29; N, 2.44.

(2*S*,3*R*,4*S*,4a*R*)-2-((Isopropyldimethylsilyl)oxy)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-2,3,4,4a-tetrahydro-6-phenanthridone (25). Carbamate **24** (61 mg, 0.108 mmol) was diluted with a mixture of ethanol (2 mL) and cyclohexadiene (4 mL). Palladium over carbon (50 mg) was added, and mixture was refluxed for 2 h and then filtered to give 46 mg (0.106 mmol, 99%) of compound **25**: R_f 0.37 (hexane/ethyl acetate, 1:1); $[\alpha]^{20}_D$ +30.3° (*c* 1.1 $CHCl_3$); IR (neat) *ν* 3381, 2936, 1678, 1477, 1256, 1062, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.60 (1H, s), 7.03 (1H, s), 6.28 (1H, br s), 6.19 (1H, t, *J* = 3 Hz), 6.04 (1H, d, *J* = 2 Hz), 6.03 (1H, d, *J* = 2 Hz), 4.31 (1H, m), 4.08 (3H, m), 1.51 (3H, s), 1.36 (3H, s), 1.02 (7H, m), 0.17 (6H, s); ^{13}C NMR ($CDCl_3$) *δ* 162.27 (CO), 151.67 (C), 148.51 (C), 128.5 (C), 127.1 (C), 127.06 (CH), 126.02 (2CH), 121.1 (C), 110.84 (C), 107.68 (CH), 101.79 (CH_2), 101.36 (CH), 79.53 (CH), 79.11 (CH), 73.33 (CH), 55.68 (CH), 27.18 (CH_3), 24.88 (CH_3), 16.83 (CH_3), 14.61 (CH_3), −3.7 (CH_3), −4.03 (CH_3); MS (CI, 70 eV) *m/z* (relative intensity) 432 (M + 1, 50), 331 (25), 266 (30), 119 (100). Anal. Calcd for $C_{22}H_{29}O_6N$: C, 61.23; H, 6.77; N: 3.25. Found: C, 61.27; H, 6.77; N, 3.28.

(2*S*,3*R*,4*S*,4a*R*)-8,9-(Methylenedioxy)-2,3,4-trihydroxy-2,3,4,4a-tetrahydro-6-phenanthridone: (+)-Lycoricidine (4a). Trifluoroacetic acid (2 mL) was added to acetonide **25** (25 mg, 0.057 mmol) in an ice-cooled bath. The solution was stirred for 20 min, and 14 mg (0.049 mmol, 85%) of triol **4** was obtained after the solvent was removed: R_f 0.4 (CH_3Cl/MeOH, 4:1); $[\alpha]^{20}_D$ +170.0° (*c* 1, CH_3OH); IR (neat) *ν* 3392, 2924, 1681, 1477, 1207, 1154 cm^{-1}; ^1H NMR (CD_3OD) *δ* 7.31 (1H, s), 7.06 (1H, s), 6.07 (br t), 5.96 (2H, d, *J* = 6 Hz), 4.30 (br d), 4.16 (br d), 3.83

(2H, m); ^{13}C NMR (CD_3OD) δ 166.58 (CO), 153.38 (C), 150.14 (C) 132.53 (C), 123.49 (CH), 123.49 (C), 107.81 (CH), 104.40 (CH), 103.53 (CH_2), 74.41 (CH), 71.06 (CH), 54.02 (CH).

Diels–Alder Adduct of 1,2-*cis*-(Isopropylidenedioxy)-3-chloro-3,5-cyclohexadiene (6b) with Benzyne (31). To a two-necked flask fitted with an addition funnel and a reflux condenser was added a solution of **6b** (502 mg, 3.01 mmol) dissolved in dimethoxyethane (DME, 5.5 mL). Isoamyl nitrite (960 mg, 8.2 mmol) was added, and the reaction was brought to reflux. A solution of anthranilic acid dissolved in DME (5.5 mL) 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 Et_2O (25 mL), and washed with 5% aqueous NaOH. The aqueous layer was extracted with Et_2O (3 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated at reduced pressure. Chromatography (silica, hexane/ethyl acetate, 25:1) yielded 521 mg of a pale yellow oil (66%): R_f 0.18 (hexane/ethyl acetate, 25:1); $[\alpha]^{25}_D$ +59.7° (*c* 0.83, $CHCl_3$); IR (neat) ν 2995, 2940, 1620, 1470, 1270, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.44 (s, 3H), 4.13 (m, 1H), 4.22 (dd, 1H, J = 7.0, 1.2 Hz), 4.36 (ddd, 1H, *J* = 7.1, 3.6, 1.1 Hz), 6.43 (m, 2H), 7.22 (m, 3H), 7.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 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, 139.6; MS (CI, 70 eV) *m/z* (relative intensity) 263 (M + 1) (25), 247 (20), 233 (15), 205 (100); HRMS calcd for $C_{15}H_{16}ClO_2$ 263.0839, found 263.0843, error 1.7 ppm. Anal. Calcd for $C_{15}H_{15}ClO_2$: C, 68.57; H, 5.75. Found: C, 68.50; H, 5.78.

Diels–Alder Adduct of 1,2-*cis*-(Isopropylidenedioxy)-3-chloro-3,5-cyclohexadiene with Benzoquinone (32). Benzoquinone (483 mg, 4.47 mmol) was added to a stirred solution of **6b** (554 mg, 2.98 mmol) in benzene (15 mL). The solution was heated at reflux, and after 22 h it was cooled to room temperature. The solid precipitate was filtered to yield 464 mg of a pale yellow amorphous solid (53%): R_f 0.20 ($CHCl_3$/MeOH, 100:1); mp 196.5–197.5 °C; $[\alpha]^{25}_D$ −155.8° (*c* 0.62, $CHCl_3$); IR (KBr) ν 3000, 1730, 1620, 1390, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.34 (s, 3H), 2.88 (d, 1H, *J* = 8.8 Hz), 2.98 (dd, 1H, *J* = 8.8, 2.7 Hz), 3.46 (m, 1H), 4.28 (d, 1H, *J* = 7.0 Hz), 4.40 (dd, 1H, *J* = 7.1, 2.8 Hz), 6.06 (m, 2H), 6.63 (d, 1H, *J* = 10.5 Hz), 6.74 (d, 1H, *J* = 10.5 Hz); ^{13}C NMR ($CDCl_3$) δ 25.1, 25.3, 40.2, 45.9, 51.2, 67.7, 77.6, 84.3, 110.2, 130.5, 133.7, 141.8, 143.0, 193.2, 195.9; MS (CI) *m/z* (relative intensity) 295 (M + 1) (10), 279 (6), 267 (6), 259 (8), 237 (8), 59 (100); HRMS calcd for $C_{15}H_{16}ClO_4$ 295.0737, found 295.0725, error 3.9 ppm. Anal. Calcd for $C_{15}H_{15}ClO_4$: C, 61.13; H, 5.13. Found: C, 61.16; H, 5.11.

Diels–Alder Adduct of 1,2-*cis*-(Isopropylidenedioxy)-3-chloro-3,5-cyclohexadiene with Napthoquinone (33). Napthoquinone (689 mg, 4.35 mmol) was added to a stirred solution of **6b** (578 mg, 3.11 mmol) in 1,4-dioxane (15 mL), and the solution was heated at reflux. After 22 h, the solution was diluted with Et_2O (20 mL) and washed with water (20 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography (silica, hexane/ethyl acetate, 10:1 to 4:1) yielded 430 mg of a white crystalline compound (40%): R_f 0.16 (hexane/ethyl acetate, 4:1); mp 181–182 °C; $[\alpha]^{25}_D$ −99.2° (*c* 0.6, $CHCl_3$); IR (KBr) ν 2950, 1680, 1595, 1375 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.32 (s, 3H), 3.10 (d, 1H, *J* = 9.0 Hz), 3.21 (dd, 1H, *J* = 9.0, 2.8 Hz), 3.54 (dddd, 1H, *J* = 6.2, 3.1, 3.1, 1.2 Hz), 4.35 (dd, 1H, *J* = 7.0, 1.4 Hz), 4.48 (ddd, 1H, *J* = 7.1, 3.1, 1.2 Hz), 5.79 (dd, 1H, *J* = 8.6, 0.61 Hz), 5.91 (ddd, 1H, *J* = 8.6, 6.4, 1.1 Hz), 7.68 (m, 2H), 7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.1, 25.3, 40.7, 46.9, 52.3, 67.9, 77.8, 84.3, 110.2, 126.3, 126.9, 130.4, 133.6, 134.1, 134.6, 136.0, 137.1, 193.1, 195.0; MS (EI) *m/z* (relative intensity) 345 (M$^+$, 2), 329 (20), 286 (35), 104 (100); HRMS calcd for $C_{19}H_{18}ClO_4$ 345.0894, found 345.0903, error 2.80 ppm. Anal. Calcd for $C_{19}H_{17}ClO_4$: C, 66.19; H, 4.97. Found: C, 66.09; H, 4.95.

Photoadduct of 6b with Benzoquinone (34). To a solution of protected chlorodiol (301 mg, 1.62 mmol) in benzene (10 mL, degassed) was added 1,4-benzoquinone (192 mg, 1.78 mmol). The solution was stirred until the 1,4-benzoquinone was dissolved, and then it was introduced by means of a cannula into a quartz photolysis apparatus. The yellow solution was photolyzed at 3600 Å. After 11 h, the reaction mixture was diluted with Et_2O (25 mL) and washed with brine (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude amorphous solid was chromatographed (silica, hexane/ethyl acetate, 10:1) to yield 75 mg of a yellow oil (16%): R_f 0.20 (hexane/ethyl acetate, 15:1); $[\alpha]^{25}_D$ +163.8° (*c* 0.57, $CHCl_3$); IR (CCl_4) ν 3005, 1680, 1640, 1360, 1390 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.42 (s, 3H), 3.76 (d, 1H, *J* = 6.0 Hz), 4.43 (dd, 1H, *J* = 5.6, 0.8 Hz), 4.83 (m, 1H), 5.59 (ddd, 1H, *J* = 10.4, 5.6, 2.0 Hz), 6.04 (dt, 1H, *J* = 10.4, 0.8 Hz), 6.20 (dd, 1H, *J* = 10.2, 2.0 Hz), 6.26 (dd, 1H, *J* = 10.4, 2.0 Hz), 6.65 (dd, 1H, *J* = 10.4, 3.2 Hz), 7.82 (dd, 1H, *J* = 10.4, 3.2 Hz); ^{13}C NMR ($CDCl_3$) δ 26.7, 27.9, 51.3, 72.6, 75.8, 79.7, 101.9, 110.7, 120.1, 128.7, 130.9, 131.5, 143.6, 146.1, 184.0; MS (CI, 70 eV) *m/z* (relative intensity) 295 (M + 1) (15), 259 (15), 237 (50), 201 (100); HRMS calcd for $C_{15}H_{15}ClO_4$ 294.0659, found 294.0658, error −0.4 ppm.

(3a*R*,4*S*,5*S*,7a*S*)-6-Chloro-4,5-(Isopropylidenedioxy)-3-methyl-3a,4,5,7a-tetrahydro-1,2-benzisoxazole (35). Phenyl isocyanate (636 mg, 5.38 mmol) was added to a stirred solution of **6b** (1.0 g, 5.38 mmol), nitroethane (408 mg, 5.38 mmol), and a catalytic amount of triethylamine (3 drops) in benzene (6 mL). Additional phenyl isocyanate (2 equiv) in nitroethane containing 6 drops of triethylamine was added in two increments at 2 h and 15 h. After 27 h, the reaction mixture was washed with water (2 × 20 mL) and 10% aqueous NaOH (10 mL). The benzene solution was dried over $MgSO_4$ and concentrated under reduced pressure to give a brown crystalline solid. Recrystallization (hexane/ethyl acetate, 6:1) yielded 955 mg of a white crystalline solid (73%): R_f 0.17 (hexane/ethyl acetate, 4:1); mp 152153.5 °C; $[\alpha]^{25}_D$ +285.2° (*c* 0.54, $CHCl_3$); IR (KBr) ν 3005, 2950, 1660, 1632, 1115, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.40 (s, 3H), 2.00 (d, 3H, *J* = 1.2 Hz), 3.80 (dd, 1H), 4.35 (d, 1H, 4.9 Hz), 4.60 (dd, 1H, *J* = 5.0, 3.1 Hz), 5.12 (ddd, 1H, *J* = 9.0, 3.2, 1.0 Hz), 5.80 (dd, 1H, *J* = 3.3, 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 12.5, 26.4, 27.6, 49.2, 72.5, 72.7, 75.0, 110.2, 123.2, 135.2, 154.2. Anal. Calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; N, 5.75. Found: C, 54.20; H, 5.80; N, 5.76.

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