(±)-Methyl 7-[6-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-octenyl]-2,2-dimethyl-3aβ,5β,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-5-yl]-5-heptynoate (34). To the vinyllithium reagent **24** [from the transmetalation of the vinyltin reagent **23** (0.52 g, 0.98 mmol)] in dry THF (4 mL) at −78 °C was added a solution of CuI·Bu_3P (0.31 g, 0.78 mmol) and Bu_3P (0.19 mL, 0.78 mmol) in dry THF (2 mL). After the mixture was stirred at −78 °C for 30 min, a solution of enone (±)-**1** (0.11 g, 0.71 mmol) in dry Et_2O (2 mL) was added. The reaction mixture was stirred at −78 °C for 10 min and at −30 °C for 1 h. HMPA (0.25 mL, 1.43 mmol) and a solution of propargyl iodide **21** (0.30 g, 1.13 mmol) in dry THF (1 mL) were added, and the mixture was stirred at −30 °C for 3 h. The usual workup, followed by flash chromatography with 15:1 hexane/EtOAc, gave the unalkylated product **11** (0.087 g, 18%), the cis alkylated product (8-*epi*-**34**) (0.150 g, 39%), and the desired **34** (0.153 g, 40%; an inseparable mixture of two diastereomers) as a colorless oil: IR (neat) 2960 (s), 2940 (s), 2860, 1760 (s), 1745 (s), 1465, 1440, 1375, 1250, 1215, 1160, 1070, 970, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (m, J = 15 Hz, H13 and H14), 4.57 (m, H10 and H11), 4.16 (m, H15), 3.71 (s, 3 H), 2.99 (m, H12), 2.48 (m, 3 H), 2.44 (t, J = 7.4 Hz, 2 H), 2.22 (tt, J_1 = 6.9 Hz, J_2 = 2.0 Hz, 2 H), 1.81 (p, J = 7.2 Hz, 2 H), 1.49–1.23 (m, 8 H), 1.45 (s, 3 H), 1.39 (s, 3 H), 0.93 (m, 12 H), 0.06 (2 s, 6 H); ^{13}C NMR ($CDCl_3$) δ 211.56*,[48] 173.57, 136.34*, 128.44*, 112.88*, 80.69, 80.60, 79.19, 77.07, 72.88, 51.72, 51.43, 46.18*, 38.21, 32.82, 31.74, 27.01, 25.85, 25.40, 24.92, 24.81, 24.06, 22.55, 18.38, 18.21*, 13.95, −4.24, −4.75; HRMS, m/z 534.3372 (calcd for $C_{30}H_{50}O_6Si$ 534.3376). The cis alkylation product was equilibrated as described above for 8-*epi*-**25**, and the mixture was flash chromatographed (15:1 hexane/EtOAc) to give 0.072 g (19%) of **34**, for an overall yield of 0.225 g (59%) of **34**.

Desilylation of 34. (±)-Methyl 7-[6-((1*E*)-3-Hydroxy-1-octenyl)-2,2-dimethyl-3aβ,5β,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-5-yl]-5-heptynoate (35). Silyl ether **34** (0.090 g, 0.168 mmol) was stirred in CH_3CN (3 mL) and cooled to 0 °C. Pyridine (0.10 mL) was added, followed by 50% aqueous HF (0.30 mL). The reaction mixture was warmed to room temperature and stirred for 3 h. The mixture was worked up in the same manner as described above to give crude **35** (0.068 g, 96%). Flash chromatography with 2:1 hexane/EtOAc furnished **35** (a mixture of two diastereomers) as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.77 (m, J = 15 Hz, 2 H), 4.55 (m, H10 and H11), 4.18, (m, H15), 3.72 (s, 3 H), 2.97 (m, J = 3 Hz, H12), 2.51 (m, 3 H), 2.43 (t, J = 7.4 Hz, 2 H), 2.22 (tt, J_1 = 6.9 Hz, J_2 = 2.3 Hz, 2 H), 1.80 (p, J = 7.2 Hz, 2 H), 1.73–1.18 (m, 9 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 0.91 (t, 3 H).

Aluminum Amalgam Reduction of 35. (±)-5,6-Didehydroprostaglandin E_2 Methyl Ester (36) and (±)-5,6-Dihydro-15-*epi*-prostaglandin E_2 Methyl Ester (37). Ketone **35** (18 mg, 0.043 mmol) was submitted to the usual Al(Hg) reduction conditions described above. After a total of 26 h, the reaction mixture was worked up to give a mixture of diols **36** and **37** (15 mg, 96%): R_f 0.19 and 0.29 (2:1 EtOAc/hexane), respectively;[31a,41] ^1H NMR ($CDCl_3$) δ 5.78 (2 dd, J_1 = 15.3 Hz, J_2 = 6.6 Hz and 5.9 Hz, 1 H), 5.64 (2 dd, J_1 = 15.3 Hz, J_2 = 8.3 Hz, 1 H), 4.17 (m, H11 and H15), 3.72 (s, 3 H), 2.81 (dd, J_1 = 18 Hz, J_2 = 7 Hz, 1 H), 2.73 (m, 2 H), 2.44 (t, J = 7 Hz, 2 H), 2.40–2.03 (m, 7 H), 1.83 (p, J = 7 Hz, 2 H), 1.67–1.23 (m, 8 H), 0.91 (t, 3 H); HRMS (CI conditions), m/z 365.2332 (calcd for $C_{21}H_{33}O_5$ (M + H) 365.2328). The product mixture was not further purified.

Acknowledgment. The early developmental work on the enone **1** was supported by a grant from the National Science Foundation and was based on studies in our labs by Dr. Kevin B. Kunnen whose contributions were gratefully acknowledge. The application of the enone to the synthesis of prostanoids was supported by a grant from the National Institutes of Health.

Supplementary Material Available: General experimental information, experimental procedures, and spectral data on **13**, **14**, and **16** plus various byproducts (eq 2) (5 pages). Ordering information is given on any current masthead page.

Enantioselective Synthesis through Microbial Oxidation of Arenes.[1] 1. Efficient Preparation of Terpene and Prostanoid Synthons

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Abstract: *cis*-Toluenediol obtained by the microbial degradation of toluene by *Pseudomonas putida 39D* was shown to be a versatile chiral pool substrate in the formal total synthesis of $PGE_2\alpha$. Diol **1** was converted to enone **5** in three steps in an overall yield of 45%. A method for reliable oxidative cleavage of 1,3-dienes to 1,4-dicarbonyl compounds was implemented. Other transformations of **1** leading to terpenoid or cyclohexene oxide synthons **6**, **7**, and **4a** were also addressed. The isolation of three new arene diols, namely **28–30**, available via microbial oxidation of chlorobenzene, styrene, and phenylacetylene is reported, and their utility in the synthesis of functionalized cyclohexene oxides is indicated.

In 1970 Gibson and co-workers reported the enantioselective oxidation of toluene to *cis*-toluenediol (**1**) by a mutant of *Pseudomonas putida*, a soil bacterium.[3] Since that time many other simple arenes were shown to yield diols of this type through microbial oxidation techniques.[4] The possibility of utilizing arenes that are widely regarded as environmental pollutants in the preparation of optically pure natural products seemed intriguing, and we chose *cis*-toluenediol (**1**) as the initial substrate because

(1) Presented in part at the 194th National Meeting of the American Chemical Society, Denver, CO, April 1987, Abstract 28.

(2) Recepient of the National Institute of Health Research Career Development Award, 1984–1989.

(3) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J. *Biochemistry* **1970**, *9*, 1626. Diol **1** is now manufactured by ICI Pharmaceuticals and is available in multigram quantities [ICI Fine Chemicals, P.O. Box 42 Hexagon House, Blackley, Manchester M9 3DA, England].

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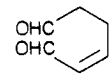
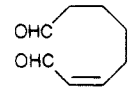
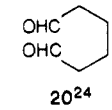
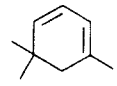
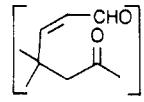
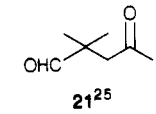
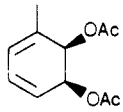
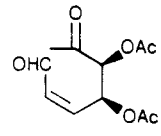
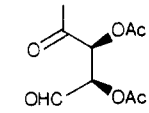
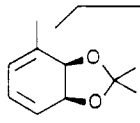
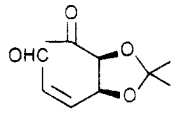
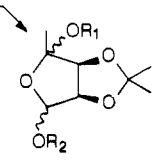
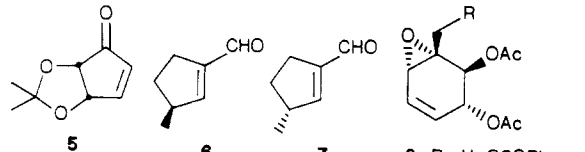
0002-7863/88/1510-4735$01.50/0

Table I

diene	cond	olefin	cond	dicarbonyl	yield, %
 9[21]	1.5 mmol of satd sol of O_3 in CH_2Cl_2 at −78 °C	 14	CH_2Cl_2, −78 °C excess O_3	 19[23]	70[a]
 10[21]	1.5 mmol of satd sol of O_3 in CH_2Cl_2 at −78 °C	 15[26]	CH_2Cl_2, −78 °C excess O_3	 20[24]	89[a]
 11[22]	CH_2Cl_2, −78 °C excess O_3	 16 not isolated		 21[25]	52
 12[3]	1.5 mmol of satd sol of O_3 in CH_2Cl_2 at −78 °C	 17	CH_2Cl_2, −78 °C excess O_3	 2b	50
		EtOAc, −60 °C, excess O_3			
 13	1.5 mmol of satd sol of O_3 in CH_2Cl_2 at −78 °C	 18	CH_2Cl_2 or CH_2Cl_2/MeOH, −78 °C excess O_3	 22 22a: $R_1=R_2=H$ b: $R_1=H; R_2=Me$ c: $R_1=R_2=Me$	60–70

[a] Isolated as the corresponding diol.

of the relatively rich repertoire of strategies that could be employed in its further functionalization. Three such strategies are outlined in Figure 1. The first of these (path a) involves retaining the diol moiety while oxidatively cleaving the conjugated diene to a 1,4-dicarbonyl system. The second (path b) would dictate cleavage of the diol itself while transferring its chirality to another position of the incipient 1,6-dicarbonyl compound. The third approach would stem from the use of the diol moiety to direct further functionalization of the six-membered ring through processes such as epoxidation, Ireland–Claisen rearrangement, or Diels–Alder reactions, which would utilize one of the diols as either a tether or a directing group. In this paper we report on the application of these three strategies to the preparation of enone **5**, an intermediate in prostaglandin syntheses, aldehydes **6** and **7**, potential synthons for perhydroazulene terpenes, and cyclohexene oxide **4a**, the descarbobenzoxy derivative of crotepoxide **8**. Central to the



oxidative cleavage of dienes will be a newly established ozonolysis procedure for conjugated dienes.

Prostaglandin Synthon 5. This compound and its derivatives have recently been prepared by several approaches, including those that produced the desired enantiomer.[5-8] Our approach required

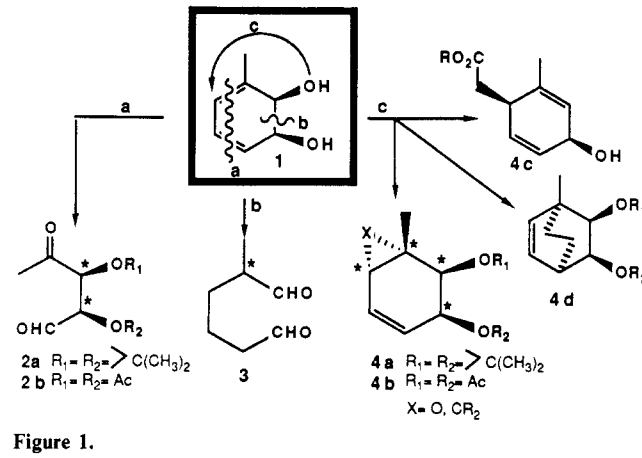


Figure 1.

that an efficient cleavage of the 1,3-diene system in **1** in an oxidative fashion be available to produce keto aldehyde **2**. The review of literature indicated that direct ozonolysis of 1,3-dienes frequently leads to undesired rearrangement products of allylic ozonides.[9-12]

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Because the literature precedent regarding a reliable provision of dicarbonyl compounds from 1,3-dienes seemed uncertain and sketchy, we undertook a study of several simple dienes to determine the feasibility of such oxidative transformations. The summary of our results is shown in Table I.

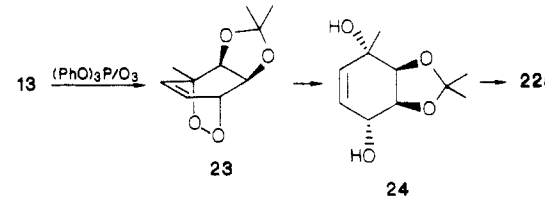
Several solvents and varying workup procedures have also been used during the optimization experiments. We found that the conjugated dienes could be ozonized *quantitatively* in a *stepwise manner* to yield initially those dicarbonyl compounds resulting from the attack of ozone at the more substituted olefinic site. These compounds, namely **14–18**, were then subjected to iterative procedure to yield the final dicarbonyl products representing the total cleavage of the conjugated diene systems.

Direct ozonolysis of dienes also furnished the dicarbonyl substrates **19–21**, **2**, and **22**, provided that the time and the flow of ozone were most carefully optimized. We did not detect any of the expected rearrangement products, and we concluded, therefore, that the literature documentation of such rearrangements reflected either special cases of substrates that were stereoelectronically biased or that such rearrangements were due to uncontrolled or unoptimized experimental procedures.

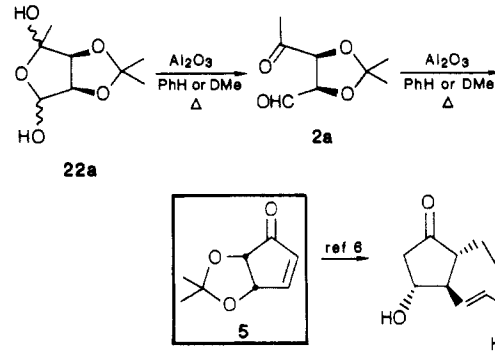
Thus either or both olefinic sites in a conjugated diene may be oxidatively cleaved in a reliable fashion. In all but one case the initial dicarbonyl compounds resulting from the cleavage of the more substituted olefin were easily isolated. In the case of acetonide **13**, keto aldehyde **18** was detected and identified but was used directly in further oxidation to produce **22**, which was eventually prepared on large scale by using excess ozone in ethyl acetate. By contrast, diacetate **12** was ozonized to a stable, isolable keto aldehyde **17**. Any or all of the hemiacetals **22** were accessible as a function of the amount of methanol used. Because the presence of diastereomers complicated the spectral analysis of these compounds, these substrates were immediately converted to either **2a** or **5**. On several occasions a pure diastereomer of **22** was isolated but upon its ^{1}H NMR analysis in solution equilibrated to the original mixtures. The yields and reproducibility index of the reactions in Table I were found satisfactory.

In addition to the ozonolysis procedure, chemically generated singlet oxygen[13,15] was used to prepare the endocyclic peroxide **23** from protected diol **13a** as shown. Reduction of the endoperoxide followed by OsO_4/IO_4^- cleavage gave hemiacetal **22a** in an overall yield comparable to the ozonolysis procedure (see the Experimental Section). It should be noted that **24** could be used to manufacture various cyclohexene oxides by further functionalization.

Hemiacetals **22a**, **22b**, and **22c** were converted to keto aldehyde **2a** by carefully controlled dehydration on neutral alumina in



benzene or dimethoxy ethane. It is interesting to note that keto aldehyde **2b** exists exclusively in the open form, whereas **2a** prefers to exist in the hydrated cyclic version. Neither, however, underwent the expected aldol condensation under standard base-catalyzed conditions. This observation has been made previously and has been rationalized by conformational freedom of the ketone/aldehyde functionalities.[14] Successful aldol-type reactions usually required further activation of the methyl ketone by phosphonate functionalities, as in the approaches of Borchardt[8] and Liu,[27] or they demanded in situ generation of the enolate anion.[7] Exposure of aldehyde **2a** to excess alumina in refluxing benzene or refluxing dimethoxyethane brought about a clean, essentially quantitative conversion of **2a** to the desired enone **5**.[28,29] Since this compound was previously converted to prostaglandins, this accomplishment constituted a formal synthesis of $PGE_2\alpha$. In



the second generation synthesis of this enone, crude diol **1**, generated from toluene in a yield of 3000 mg/L of culture was protected and ozonized to **22a** in 70% yield. Exposure of **22a** to excess alumina in refluxing benzene or DME gave **5** in 65% isolated yield.[29] Thus the preparation of a prostaglandin intermediate was accomplished in *three operations from toluene* in an enantioselective fashion and an *overall yield of 45%*, where the only purification need be either the final distillation or crystallization of enone **5**.

Other Functionalization of Arenediol 1 (Paths b and c). Catalytic hydrogenation of **1** gave a mixture of diols **25** (path b). No attempts were made to control this hydrogenation because both compounds were desired; in fact, because the separation of these compounds is facile, a 1:1 mixture would be ideal to provide both enantiomeric series, as these diols might prove to be useful chiral protecting groups. Diols **25** were separated by chromatography on silica gel via their monobenzoates, and the cleavage to dialdehydes was accomplished with HIO_4.[16] The aldehydes **6** and **7** were then generated by the known procedure.[18] Improvements in the condensation were attained by enamine condensation in HOAc, reported by White and used previously in

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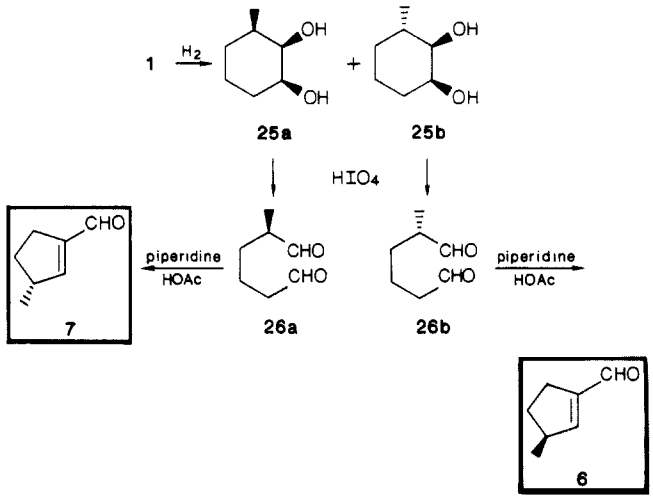
(27) Lim, Mu-I.; Marquez, V. E. *Tetrahedron Lett.* **1987**, *28*, 5559.

(28) The aldol-type condensation of carbonyl compounds with alumina has been reported. See, for example: Hudlicky, T.; Srnak, T. *Tetrahedron Lett.* **1981**, *22*, 3351. Muzart, J. *Synthesis* **1982**, 60. Posner, G. H. *Angew. Chem.* **1978**, *90*, 527; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487.

(29) The aldol condensations were quantitative by GC/TLC/NMR methods. However, the mass balance in most reactions was consistantly 60–65%. A study of some detail has been performed in the attempt to optimize the mass balance and to provide alumina of known and reproducible activities. It is our feeling that the products of Al_2O_3 catalyzed reactions are retained irreversibly on alumina or that they polymerize to the extent of the observed ~30% loss of mass. Such observations have been noted by others.[28] We will report on the optimization of mass balance recovery in the near future.

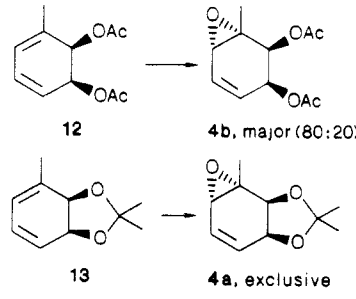
(30) The chemistry described in this article is the subject of a patent application, Virginia Tech, Spring 1988.



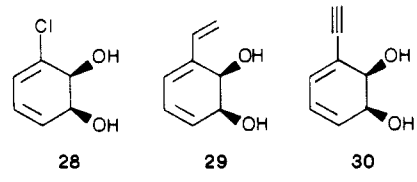
preparation of cyclopentenyl carboxaldehydes.[17,18] These aldehydes possess the α and β configurations of the secondary methyl group in bulnesene and kessane sesquiterpenes, respectively, and could be in principle, used in chiral syntheses of these terpenes.

The functionalization of the diene unit in **1** (path c) is possible through several simple processes. The Diels–Alder reaction leading to bicyclo[2.2.2]octane systems **4d** is facile and was reported in the literature in the context of the structure elucidation of arene diols.[3] A Diels–Alder strategy that would yield compounds of zeylena type is planned form intermediates of type **28–30**, in which additional means of functionalization at the benzylic carbon become available.

The epoxidation of **12** or **13** with buffered *m*-CPBA (pH 8) led to monoepoxides **4** (80:20 mixture), with much better control of stereochemistry in the case of acetonide **13** whose epoxidation gave a single isomer.[19] This finding bodes well for our planned



synthesis of various cyclohexane oxides derivatives from compounds suitably functionalized at the benzylic site. To this end several other arenes were subjected to the microbial oxidation procedure to yield diols **28–30** in the yields of 1000, 1000, and



50 mg/L of culture, respectively. All of these materials contain latent functionality that will permit their conversion to the benzyl esters required for elaboration to cyclohexane oxides. The Mitsunobu inversion[20] of the hydroxyls at C-3 and the conversion of **28–30** to zeylena, senepoxides, and other cyclohexene oxides, as well as other suitable targets, form the basis of our current endeavors aimed at the synthesis of biologically active compounds via the tandem methodology involving microbial transformations and chemical synthesis.

Conclusion

cis-Toluene diol (**1**) was shown to be a versatile substrate in the chiral syntheses of several intermediates of biological significance. The conditions of reliable oxidative cleavage for 1,3-dienes were implemented, and a chiral prostaglandin synthon **5** was prepared from toluene in three steps. The transition from toluene to other more functionalized arenes will make possible such endeavors as the synthesis of cyclohexane oxides, compounds of significant antitumor properties.

Experimental Section

(2*R*,3*S*)-2,3-Dihydroxy-1-methylcyclohexa-4,6-diene (1).[3] *P. putida 39D* was grown at 28 °C in MBS–arginine medium,[3] and the culture (80 mL) was incubated in a 250-mL Erlenmeyer flask. Toluene was supplied by a scale bulb attached to the flask by a neoprene stopper, and the culture was aereated on a reciprocal shaker. After 6 h, the culture was placed in a 1-L Erlenmeyer flask and medium was added until the total volume was 400 mL. A stream of air/toluene (5:1, volume) was bubbled for 24 h (total volume of toluene consumed was 20 mL). The culture was centrifuged at 5000 rpm during 10 min, and the pH of the medium was adjusted to 8.4 with NaOH. The medium was saturated with NaCl, centrifuged again, and extracted with ethyl acetate (acid-free, 5 × 100 mL). The organic extract was dried with Na_2SO_4, and the solvent was evaporated. The crude diol was chromatographed (10% deactivated silica gel, methylene chloride/acetone, 2:1) to give 1.5 g of pure **1** (yield 3 g/L of culture); $[\alpha]^{25}_D$ +26.4° (*c* 0.38, CH_3OH); R_f 0.2 (hexane/ethyl acetate, 2:1); IR ($CHCl_3$) 3575, 3400–3200, 1400, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (3 H, s), 2.18 (2 H, m), 3.96 (1 H, m), 4.22 (1 H, m), 5.75 (d br, J = 7 Hz, 1 H), 5.80 (dd, J_1 = 14, J_2 = 4 Hz, 1 H), 5.95 (ddd, J_1 = 14, J_2 = 7, J_3 = 2 Hz, 1 H).

In a similar fashion, chlorobenzene, styrene, and phenylacetylene were converted to diols **28–30**, respectively.

(2*R*,3*S*)-2,3-Dihydroxy-1-chlorocyclohexa-4,6-diene (28).[3,4b] *P. putida 39D* was grown at 28 °C in MBS–arginine medium (75 mL) in a 250-mL Erlenmeyer flask. Toluene was supplied by a scale bulb attached to the flask by a neoprene stopper, and the culture was aereated on a reciprocal shaker. After 6 h the culture was centrifuged at 5000 rpm during 10 min, the medium was discarded, and the cells were suspended in 400 mL of fresh MBS–arginine medium and placed in a 1-L Erlenmeyer flask equipped with a bubbler. A stream of air/chlorobenzene (5:1 by volume) was bubbled through the medium controlled by a thermostat at 28–29 °C. After 24 h the culture was centrifuged, the cells were discarded, and the pH of the medium was adjusted to 8.4 with aqueous NaOH. The solution was saturated with NaCl, centrifuged again, and extracted with ethyl acetate (acid-free, 5 × 100 mL). The organic extract was dried with Na_2SO_4, and solvent was evaporated and filtered through a small plug of silica gel (10% deactivated, hexane/ethyl acetate, 1:1) to give pure **28** as a white solid (0.40 g), mp 82–84 °C: R_f 0.32 (hexane/ethyl acetate, 1:1); ^1H NMR ($CDCl_3$) δ 2.63 (d, J = 8.4 Hz, 1 H), 2.74 (d, J = 7.3 Hz, 1 H), 4.19 (t, J = 7.3 Hz, 1 H), 4.48 (m, 1 H), 5.87 (m, 2 H), 6.12 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 69.1 (CH), 71.4 (CH), 122.7 (CH), 123.4 (CH), 128.0 (CH), 134.9 (C).

(2*R*,3*S*)-2,3-Dihydroxy-1-vinylcyclohexa-4,6-diene (29). Via the same procedure as for chlorobenzene, 0.48 g of crude diol **29** was obtained after solvent evaporation of the organic extract. Column chromatography of the crude product (10% deactivated silica gel, hexane/ethyl acetate, 1:1) afforded 0.39 g of pure **29** as a white very unstable solid: R_f 0.35 (hexane/ethyl acetate, 1:1); ^1H NMR ($CDCl_3$) δ 1.90 (br d, 1 H), 2.80 (br d, 1 H), 4.35 (m, 1 H), 4.45 (m, 1 H), 5.19 (d, J = 11 Hz, 1 H), 5.48 (d, J = 18 Hz, 1 H), 5.82 (m, 1 H), 5.95 (m, 1 H), 5.98 (m, 1 H), 6.38 (dd, J_1 = 11, J_2 = 18 Hz, 1 H). Note: Due to the unstability of this solid (it polymerized rapidly at room temperature), the melting point could not be taken.

(2*R*,3*S*)-2,3-Dihydroxy-1-ethynylcyclohexa-4,6-diene (30). *P. putida 39D* was grown at 28 °C in MBS–arginine medium, and the culture (80 mL) was incubated in a 250-mL Erlenmeyer flask. Toluene was supplied by a scale bulb attached to the flask by a neoprene stopper, and the culture was aereated on a reciprocal shaker. After 6 h, the culture was centrifuged at 5000 rpm for 10 min, the medium was discarded, and the cells were suspended in 80 mL of fresh MBS–arginine medium. Phenylacetylene was supplied in the scale bulb, and the culture was incubated as above for 12 h. The culture was centrifuged, and the pH of the medium was adjusted to 8.4 with aqueous NaOH. The solution was saturated with NaCl, centrifuged again, and extracted with ethyl acetate (acid-free, 3 × 25 mL). The organic fraction was dried over Na_2SO_4, and solvent was removed to leave 4 mg of colorless crystals: R_f 0.27 (hexane/ethyl acetate, 1:1); ^1H NMR ($CDCl_3$) δ 2.28 (d, J = 9.6 Hz, 1 H), 2.40 (d, J = 7.7 Hz, 1 H), 3.28 (s, 1 H), 4.20–4.29 (m, 1 H), 4.32–4.40 (m, 1 H), 6.06 (s, 1 H), 6.08 (s, 1 H), 6.39 (br s, 1 H).

(2*R*,3*S*)-1-Methyl-2,3-(isopropylidenedioxy)cyclohexa-4,6-diene (13).[3] A solution of (2*R*,3*S*)-2,3-dihydroxy-1-methylcyclohexa-4,6-diene (**1**)[3] (116 mg, 0.92 mmol) in 2,2-dimethoxypropane (15 mL), with a crystal of *p*-toluenesulfonic acid, was stirred at room temperature for 10 min. Methylene chloride (20 mL) was added, and the solution was

washed with saturated $NaHCO_3$ (1 × 30 mL), 10% NaOH (1 × 30 mL), and brine (1 × 30 mL). The organic extract was dried, and the solvent was evaporated to yield 129.8 mg (85%) of **13**: R_f 0.8 (hexane/ethyl acetate, 2:1); $[\alpha]^{25}_D$ +93.74° (*c* 2.98, CH_3OH); IR (neat) 2980, 1380, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.42 (s, 3 H), 1.90 (s, 3 H), 4.45 (br d, J = 9 Hz, 1 H), 4.64 (dd, J_1 = 8.7, J_2 = 4 Hz, 1 H), 5.72 (br d, J = 5.5 Hz, 1 H) 5.80 (dd, J_1 = 9.5, J_2 = 4 Hz, 1 H), 5.95 (dd, J_1 = 9.5, J_2 = 5.5, Hz, 1 H).

(2*R*,3*S*)-2,3-Diacetoxy-4-oxopentanal (2b). Into a solution of (2*R*,3*S*)-1-methyl-2,3-diacetoxycyclohexa-4,6-diene (**12**)[3] (119 mg, 0.566 mmol) in ethyl acetate (2 mL) was passed at −78 °C a stream of O_2/O_3 until a light blue color was observed, at which time nitrogen was bubbled through for 5 min. Dimethyl sulfide (2 mL) was added dropwise at −78 °C, the temperature was raised to 0 °C, and the reaction was left stirring overnight. The solvent was removed at reduced pressure, and the residue (160 mg) was purified by Kugelrohr distillation (85–90 °C/0.005 Torr) to give 62 mg (50%) of pure **2b**: R_f 0.33 (hexane/ethyl acetate, 1:1); IR (neat) 1742, 1365, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 6 H), 2.19 (s, 3 H), 5.48 (d, J = 2.9 Hz, 1 H), 5.62 (d, J = 2.9 Hz, 1 H), 9.51 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.5, 26.83, 76.5, 77.0, 169.8, 169.5, 194.5; mass spectrum (CI), *m/e* (relative intensity) 217 (M^+ + 1, 5), 156 (100), 114 (20), 96 (15); calcd for $C_7H_9O_4$ (M − 59) 157.0501, found 157.0476.

(3*S*,4*R*)-2,5-Dihydroxy-3,4-(isopropylidenedioxy)-2-methyltetrahydrofuran (22a). A. By Ozonolysis of 13.[3] A solution of (2*R*,3*S*)-1-methyl-2,3-(isopropylidenedioxy)cyclohexa-4,6-diene (**13**)[3] (0.106 g, 0.638 mmol) in ethyl acetate (7 mL) was cooled to −78 °C and then a stream of O_2/O_3 was passed until the blue color appeared. Nitrogen was bubbled for 10 min. Dimethyl sulfide (1 mL) was added, and the temperature was allowed to rise overnight until 0 °C, whereupon the solvent was removed at reduced pressure. The residue was purified by column chromatography (10% deactivated silica gel, hexane/ethyl acetate, 9:1 to 7:3) to yield 0.067 g (56%) of a mixture of isomers: R_f 0.39 (hexane/ethyl acetate, 1:1); IR (neat) 3450, 2990, 1750, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 1.55 (s, 3 H), 3.60 (s, 1 H), 3.76 (d, J = 7.6 Hz, 1 H), 4.55 (d, J = 5.6 Hz, 1 H), 4.74 (d, J = 5.6 Hz, 1 H), 5.34 (d, J = 7.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.8 (CH_3), 24.8 (CH_3), 25.0 (CH_3), 84.0 (CH), 103.3 (CH), 108.9 (C), 112.8 (C); mass spectrum (CI), *m/e* (relative intensity) 173 (100), 155 (56), 143 (29), 129 (33), 113 (42), 87 (18); calcd for $C_7H_9O_4$ (M − 33) 157.0500, found 157.0519.

B. By $^1O_2$ Addition to 13.[3] **1,4,4-Trimethyl-3,5,8,9-tetraoxatricyclo-[2.2.2.3^{2,6}]undec-10-ene (23).** A solution of triphenylphosphite (186 mg, 0.6 mmol) in dichloromethane (15 mL) was ozonized at −78 °C until a blue color persisted. It was then purged with nitrogen for 20 min, and a solution of (2*R*,3*S*)-1-methyl-2,3-(isopropylidenedioxy)-4,6-cyclohexadiene (**13**)[3] (100 mg, 0.6 mmol) in dichloromethane (2 mL) was added. It was slowly warmed up to 0 °C and stirred for 20 min. The solvent was removed under reduced pressure, and the residue was purified by Kugelrohr distillation (80 °C/0.075 mmHg) to yield 99.8 mg (84%) of a white crystalline solid: R_f 0.79 (hexane/ethyl acetate, 8:2); mp 70–70.5 °C; IR ($CHCl_3$) 2970, 2930, 1450, 1375, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 6 H), 1.50 (s, 3 H), 4.20 (d, J = 6.9 Hz, 1 H), 4.60 (dd, J_1 = 4.5, J_2 = 6.9 Hz, 1 H), 4.8 (dt, J_1 = 1.24, J_2 = 4.5, J_3 = 6.1 Hz, 1 H), 6.30 (d, J = 8.35 Hz, 1 H), 6.50 (dd, J_1 = 6.1, J_2 = 8.35 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.1, 25.6, 25.7, 72.0, 72.6, 110.1, 130.1, 134.6.

2,8,8-Trimethyl-2,5-dihydroxy-7,9-dioxabicyclo[4.3.0]non-3-ene (24). To a solution of 1,4,4-trimethyl-3,5,8,9-tetraoxatricyclo[2.2.2.3^{2,6}]undec-10-ene (**23**) (26 mg, 0.13 mmol) in 5 mL of dry ether and 0.5 mL of methanol/water (9:1), was added aluminum amalgam (freshly prepared from 114 mg of aluminum foil and mercuric chloride). After the addition was complete, the reaction mixture was stirred for 25 min, filtered through Celite, and rinsed with ether. The ethereal solution was evaporated under reduced pressure to yield 25 mg (96%) of diol **24**. An analytical sample was obtained by flash chromatography (10% deactivated silica gel, hexane/ethyl acetate, 75:25): mp 85 °C; R_f 0.25 (hexane/ethyl acetate, 1:1); IR ($CHCl_3$) 3650, 3410, 3015, 2965, 1470, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.34 (s, 3 H), 1.38 (s, 3 H), 3.4 (s, 1 H), 3.6 (m, 1 H), 4.21 (m, 1 H), 4.29 (d, J = 7.2 Hz, 1 H), 4.48 (dd, J_1 = 7.2, J_2 = 2 Hz, 1 H), 5.98 (dd, J_1 = 9.7, J_2 = 0.8 Hz, 1 H), 6.10 (dd, J_1 = 9.7, J_2 = 5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.3 (CH_3), 25.1 (CH_3), 26.3 (CH_3), 66.1 (CH), 69.3 (C), 78.6 (CH), 81.3 (CH), 108.4 (C), 131.3 (CH), 137.9 (CH); mass spectrum (70 ev), *m/e* (relative intensity) 185 (10), 167 (6), 125 (30), 113 (57), 100 (100), 95 (30), 85 (32), 71 (35); (CI mode) 201 (4), 183 (13), 165 (13), 165 (10), 125 (100), 109 (30), 97 (33); calcd for $C_9H_{13}O_4$ (M − 15) 185.0814, found 185.0809; calcd for $C_{10}H_{17}O_4$ $(MH)^+$ (CI mode) 201.1127, found 201.1125.

(3*S*,4*R*)-2,5-Dihydroxy-3,4-(isopropylidenedioxy)-2-methyltetrahydrofuran (22a). To solution of 2,8,8-trimethyl-2,5-dihydroxy-7,9-dioxabicyclo[4.3.0]non-3-ene (**24**) (15 mg, 0.075 mmol) in dioxane (0.7 mL) and phosphate buffer (pH 8, 0.5 mL) was added a small crystal of osmium tetraoxide at 0–5 °C. After 10 min of stirring, sodium periodate (96 mg, 0.448 mmol) was added in four portions, each one after the previous one was dissolved. After 1 h of stirring, the reaction temperature was raised to room temperature, and stirring was continued for 20 h. Then 10% sodium sulfite solution (3 mL) was added, and the mixture was extracted with ether (3 × 3 mL). The organic layer was washed with saturated sodium bicarbonate solution and brine and dried over sodium sulfate, and the solvent was removed to yield 11 mg (81%) of a homogeneous material whose spectral data matched that of **22a**.

(3*S*,4*R*)-2-Hydroxy-3,4-(isopropylidenedioxy)-2-methyl-2-methoxytetrahydrofuran (22b). Into a solution of (2*R*,3*S*)-1-methyl-2,3-(isopropylidenedioxy)-4,6-cyclohexadiene (**13**)[3] (200 mg, 1.2 mmol) in MeOH (20 mL) at −78 °C was passed a stream of O_2/O_3 until blue color persisted, and then nitrogen was bubbled for 5 min. Dimethyl sulfide (5 mL) was added, and the temperature was raised to 0 °C. The reaction was left stirring overnight. The solvent was evaporated, and the residue was diluted with CH_2Cl_2, washed with H_2O (2 × 5 mL), and dried. Evaporation of the solvent afforded a residue, which was chromatographed (10% deactivated silica gel, hexane/ethyl acetate, 8:20) to furnish **22a–c**.

For 22b: white crystals; mp 50–51 °C; R_f 0.45 (hexane/ethyl acetate, 3:1); IR (neat) 3650–3300, 3000, 2950, 1800, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.50 (s, 3 H), 1.54 (s, 3 H), 3.15 (s, 1 H), 3.33 (s, 1 H), 3.43 (s, 3 H), 4.52 (d, J = 5.7 Hz, 1 H), 4.70 (d, J = 5.7 Hz, 1 H), 4.94 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 25.0 (CH_3), 26.3 (CH_3), 54.4 (CH_3), 55.6 (CH_3), 84.7 (CH), 85.5 (CH), 104.8 (CH), 109.5 (C), 112.8 (C); mass spectrum (CI), *m/e* (relative intensity) 205 (M^+ + 1, 2), 187 (23), 173 (100), 81 (100). Anal. Calcd for $C_9H_{16}O_5$: C, 52.94; H, 7.84. Found: C, 51.26; H, 8.07.

For (3*S*,4*R*)-3,4-(isopropylidenedioxy)-2,5-dimethoxy-2-methyltetrahydrofuran 22c: oil, R_f 0.40 (hexane/ethyl acetate, 3:1); IR (neat) 3000, 2950, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.40 (s, 3 H), 1.50 (s, 3 H), 3.23 (s, 3 H), 3.56 (s, 3 H), 4.29 (d, J = 5.8 Hz, 1 H), 4.66 (dd, J_1 = 5.8, J_2 = 3.5 Hz, 1 H), 4.71 (d, J = 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.5 (CH_3), 25.4 (CH_3), 26.1 (CH_3), 48.2 (CH_3), 58.3 (CH_3), 79.2 (CH), 84.4 (CH), 103.6 (CH), 110.8 (C), 113.3 (C); mass spectrum (CI), *m/e* (relative intensity) 217 (M^+ − 1, 8), 187 (65), 162 (18), 129 (23), 100 (53), 59 (100); calcd for $C_9H_{15}O_4$ (M − 31) 187.0970, found 187.0945.

(4*S*,8*S*)-6,6-Dimethyl-5,7-dioxabicyclo[3.3.0]oct-2-en-1-one (5). To a stirred suspension of neutral alumina (Fluka, activity V) in 70 mL of freshly distilled 1,2-dimethoxyethane (DME) was added a solution of 86.9 mg (0.457 mmol) of bis(hemiketal) **22a** in 15 mL of DME. After 15 min of reflux under argon, (2*R*,3*S*)-2,3-(isopropylidenedioxy)-4-oxopentanal (**2a**) was identified by ^1H NMR analysis as the sole product: ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 1.48 (s, 3 H), 2.33 (s, 3 H), 4.55 (d, J = 5.5 Hz, 1 H), 4.62 (d, J = 5.5 Hz, 1 H), 9.83 (s, 1 H). After 30 min of reflux under argon atmosphere, the reaction was filtered, and the solvent was removed at reduced pressure. The crude product (45.5 mg, 64.6%), 95% pure by GC (capillary column SE-30 chromosorb; 80 °C (0.5 min) to 120 °C (0.5 min) at 10 °C/min), was distilled (Kugelrohr, 40 °C/0.005 mmHg); mp 42 °C (lit.[5] mp 36–38 °C); R_f 0.37 (ethyl acetate/hexane, 1:1); $[\alpha]^{25}_D$ +62.8° (*c* 0.7, $CHCl_3$) (lit.[6] $[\alpha]^{25}_D$ +71.8° (*c* 0.91, $CHCl_3$)); IR ($CHCl_3$) 3000, 2940, 1730, 1380, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 4.46 (d, J = 5.5 Hz, 1 H), 5.27 (dd, J_1 = 5.5, J_2 = 2.2 Hz, 1 H), 6.22 (d, J = 5.9 Hz, 1 H), 7.65 (dd, J_1 = 5.9, J_2 = 2.2 Hz, 1 H). This reaction has been scaled up to 100–500-mg range. Further scale-up to multigram quantities awaits the optimization of the use and the amount of the catalyst.[29]

2-Hexenedial (14). To a solution of 1,3-cyclohexadiene[21] (240 mg, 3 mmol) in methylene chloride (5 mL) cooled to −78 °C was added dropwise a saturated solution of ozone (at −78 °C) in methylene chloride (120 mL). After addition was completed, the reaction was stirred for 10 min and dimethyl sulfide (1 mL) was added, and the mixture was stirred overnight at 0 °C. The solvent was evaporated, and the residue was dissolved in ether (20 mL), washed with water (2 × 20 mL), and dried over Na_2SO_4, and ether was evaporated. The crude product was distilled in a Krugelrohr apparatus to yield 230 mg (67%) of **14**: R_f 0.6 (hexane/ethyl acetate, 2:1); bp 60 °C/035 mmHg (Kugelrohr temperature); IR ($CHCl_3$) 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (m, 4 H), 6.15 (ddt, J_1 = 15, J_2 = 8, J_3 = 1 Hz, 1 H), 6.87 (dt, J_1 = 15, J_2 = 6 Hz, 1 H), 9.57 (d, J = 8 Hz, 1 H), 9.83 (s, 1 H); mass spectrum (CI), *m/e* (relative intensity) 113 (M^+ + 1, 100), 95 (52), 85 (22); calcd for $C_6H_9O_2$ 113.0603, found 113.0613.

2-Octenedial (15).[26] By use of an identical procedure as described for **14**, *cis*-1,3-cyclooctadiene[21] (272 mg, 2.5 mmol) was reacted with ozone to give after workup 196 mg (64%) of **15**: R_f 0.5 (hexane/ethyl acetate, 2:1); bp 120 °C/0.025 mmHg (Kugelrohr temperature); IR (neat) 3040,

2890, 2850, 1720, 1690, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (m, 2 H), 1.63 (m, 2 H), 2.33 (dq, $J_1 = 7$, $J_2 = 1.4$ Hz, 2 H), 2.47 (dt, $J_1 = 7$, $J_2 = 1.2$ Hz, 2 H), 6.09 (ddt, $J_1 = 16$, $J_2 = 8$, $J_3 = 1.4$ Hz, 1 H), 6.84 (dt, $J_1 = 16$, $J_2 = 7$ Hz, 1 H) 9.48 (d, $J = 7$ Hz, 1 H), 9.75 (t, $J = 1.4$ Hz, 1 H).

(4*S*,5*S*)-Diacetoxy-6-oxo-2-heptenal (17). To a solution of (2*R*,3*S*)-2,3-diacetoxy-1-methylcyclohexa-4,6-diene (**12**)[3] (243.5 mg, 1.16 mmol) in dichloromethane (5 mL) was added at −55 °C a saturated solution of ozone in dichloromethane (at −78 °C) (65 mL). After the addition was completed, the reaction was stirred at −55 °C for 10 min, whereupon dimethyl sulfide (3 mL) was added. The mixture was stirred overnight in an ice bath, and the solvent was evaporated under reduced pressure to give 267 mg (95%) of crude product **17**. Column chromatography (10% deactivated silica gel, hexane/ethyl acetate, 1:1) yielded 138.7 mg (65%) of pure **17**: R_f 0.33 (hexane ethyl acetate, 3:1); IR (neat) 1750, 1685, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 5.38 (d, $J = 3.5$ Hz, 1 H), 5.95 (m, 1 H), 6.27 (ddd, $J_1 = 16$, $J_2 = 8$, $J_3 = 1.5$ Hz, 1 H), 6.73 (dd, $J_1 = 16$, $J_2 = 5$ Hz, 1 H), 9.59 (d, $J = 8$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.5, 27.3, 70.8, 77.8, 133.7, 146.9, 169.1, 169.6, 192.1, 202; mass spectrum (CI), *m/e* (relative intensity) 243 ($M^+ + 1$, 10), 183 (32), 141 (53), 123 (100), 85 (20); calcd for $C_9H_{11}O_4$ (M − 59) 183.0657, found 183.05750.

(4*S*,5*S*)-4,5-(Isopropylidenedioxy)-6-oxo-2-heptenal (18). By use of an analogous procedure (2*R*,3*S*)-1-methyl-2,3-(isopropylidenedioxy)-cyclohexa-4,6-diene (**13**)[3] was reacted with ozone to give **18** as the main reaction product: R_f 0.48 (hexane/ethyl acetate, 1:1); ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 2.24 (s, 3 H), 4.66 (d, $J = 8$ Hz, 1 H), 5.1 (ddd, $J_1 = 2$, $J_2 = 8$, $J_3 = 13$ Hz, 1 H), 6.61 (ddd, $J_1 = 4$, $J_2 = 13$ Hz, 1 H), 9.56 (d, $J = 8$ Hz, 1 H).

1,4-Butanedial (19).[23] (This unstable aldehyde was reduced in situ and isolated as the corresponding diol.) A solution of 1,3-cyclohexadiene[21] (252 mg, 3.15 mmol) in methylene chloride (20 mL) was cooled to −78 °C, and a stream of O_2/O_3 was passed through until a blue color was observed, whereupon nitrogen was bubbled through for 10 min. The solution was then transferred via cannula to a suspension of $LiAlH_4$ (380 mg, 10 mmol) in ether (20 mL) under nitrogen at −10 °C. The reaction mixture was allowed to warm up and was refluxed for 15 min. After the mixture was cooled, water (0.38 mL), 10% KOH (0.76 mL), and water (0.38 mL) were added in that order, and the suspension was filtered through Celite. The solution was dried, and the solvent was evaporated to yield 198 mg (70%) of **19**: R_f 0.4 (hexane/ethyl acetate, 2:1); IR (neat) 3500–3300, 2970, 1060, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (m, 4 H), 2.6 (br s, 2 H), 3.62 (m, 4 H).

1,6-Hexanedial (20).[24] (This unstable aldehyde was reduced in situ and isolated as the corresponding diol.) By the same procedure described for **19**, *cis*-1,3-cyclooctadiene[21] (21 mg, 2 mmol) was reacted with ozone to give after workup 211.5 mg (89%) of **20**: R_f 0.3 (hexane/ethyl acetate, 1:2); IR (neat) 3400–3300, 2930, 2840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (m, 4 H), 1.58 (m, 4 H), 3.0 (br s, 2 H), 3.6 (m, 4 H).

2,2-Dimethyl-1,4-oxopentanal (21).[25] A solution of isophorone (1.382 g, 10 mmol) and tosylhydrazine (2.0 g, 1.1 mmol) in THF (30 mL) containing 3 drops of concentrated HCl was refluxed for 6 h. Benzene was added, and THF was distilled from the reaction (bp 68 °C). The temperature rose to 70 °C, and the benzene azeotrope was allowed to distill. The reaction mixture was cooled in an ice bath, and 1.5 M MeLi (30 mL, 2 mmol) was added dropwise. After 4 h the cooling bath was removed, and water was slowly added to the slurry. The reaction mixture was extracted with pentane (2 × 15 mL) and dried over $NaSO_4$, and the solvent was evaporated to give 2.1 g of crude product, which was carried on without further purification.

The crude product was dissolved in CH_2Cl_2 (20 mL), and the solution was cooled to −78 °C. A stream of O_2/O_3 was passed through until a blue color was observed, and then nitrogen was bubbled through for 5 min. Dimethyl sulfide (5 mL) was added, the reaction was allowed to warm up to room temperature, and the stirring was continued overnight. The solvent was evaporated under reduced pressure, the residue was dissolved in ether (30 mL), washed with water (2 × 20 mL), and dried, and the solvent was evaporated. The crude product was distilled in a Kugelrohr apparatus to yield 147 mg (52% overall from isophorone) of (**21**):[25] R_f 0.6 (hexane/ethyl acetate, 2:1); bp 40 °C/35 mmHg (Kugelrohr temperature); IR (neat) 1730, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 6 H), 2.14 (s, 3 H), 2.7 (s, 2 H), 9.53 (s, 1 H).

1(*S*),2(*R*)-Dihydroxy-3(*R*)-methylcyclohexane (25a) and 1(*S*),2-(*R*)-Dihydroxy-3(*S*)-methylcyclohexane (25b).[4h] (a) A solution of 1.1 g (8.8 mmol) of (2*S*,3*R*)-2,3-dihydroxy-1-methylcyclohexa-4,6-diene (**1**)[3] in 25 mL of ethyl acetate/benzene (1:1) was hydrogenated, with 5% Pd/C as catalyst, at 50 psi for 14 h. The reaction mixture was filtered, and the solvent was removed at reduced pressure. The liquid residue was purified by column chromatography (10% deactivated silica gel, hexane/ethyl acetate, 9:1) to obtain 915.5 mg (80%) of a mixture (7:3) of cis and trans methyl diols; R_f 0.16 (hexane/ethyl acetate, 1:1). This mixture was dissolved in 10 mL of dry pyridine cooled to 0–5 °C, and benzoyl chloride (0.91 mL, 7.74 mmol), also cooled to 0–5 °C, was added. After the reaction mixture was stirred overnight at room temperature, it was diluted with ether (15 mL) and washed with water (2 × 10 mL), saturated cooper sulfate solution (6 × 10 mL), and brine (2 × 10 mL). The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude mixture of monobenzoates was separated by flash chromatography (10% deactivated silica gel, hexane/ethyl acetate, 9:1), yielding 1.4 g (68%) of 1(*S*)-(benzoyloxy)-2(*R*)-hydroxy-3(*R*)-methylcyclohexane and 0.514 g (25%) of 1(*S*)-(benzoyloxy)-2(*R*)-hydroxy-3(*S*)-methylcyclohexane.

For *R* epimer: R_f 0.7 (ethyl acetate/hexane, 1:1); mp 84–85 °C; IR (HCl_3) 3620, 2930, 2870, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (d, $J = 6.8$ Hz, 3 H), 1.34–1.48 (m, 3 H), 1.58–1.98 (m, 5 H), 3.97 (br s, 1 H), 5.0 (m, 1 H), 7.44 (t, $J = 7.5$ Hz, 2 H), 7.56 (t, $J = 7.5$ Hz, 1 H), 8.4 (d, $J = 7.5$ Hz, 2 H). For *S* epimer: R_f 0.58 (ethyl acetate/hexane, 1:1); IR (neat) 3525, 2980, 2890, 1768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, $J = 6.6$ Hz, 3 H), 1.43–1.95 (m, 7 H), 2.2 (m, 1 H), 4.17 (br s, 1 H), 4.80 (dd, $J_1 = 13.0$, $J_2 = 2.6$ Hz, 1 H), 7.46 (t, $J = 7.5$ Hz, 3 H), 7.56 (t, $J = 7.5$ Hz, 1 H), 8.05 (d, $J = 7.5$ Hz, 2 H).

(b) Hydrolysis of monobenzoates (general method).[4h] To a solution of 536 mg (2.292 mmol) of the corresponding monobenzoate in methanol (5 mL) was added 0.5 mL of 10 N sodium hydroxide solution. The solution was refluxed for 1 h, and the solvent was removed at reduced pressure. The solid residue was taken up in water (15 mL) and saturated with sodium chloride, and this solution was extracted with ethyl acetate (5 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated, yielding 240.5 mg (81%) of the corresponding diol.

For 1(*S*),2(*R*)-dihydroxy-3(*R*)-methylcyclohexane (**25a**): R_f 0.32 (methanol/chloroform, 5:95); IR ($CHCl_3$) 3620, 3480, 2940, 1460, 1040, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, $J = 7$ Hz, 3 H), 1.17–1.36 (m, 3 H), 1.43–1.59 (m, 2 H), 1.59–1.74 (m, 2 H), 2.26 (br s, 2 H), 3.54 (ddd, $J_1 = 11.0$, $J_2 = 4.2$, $J_3 = 3.0$ Hz, 1 H), 3.75 (t, $J = 3$ Hz, 1 H).

For 1(*S*),2(*R*)-dihydroxy-3(*S*)-methylcyclohexane (**25b**): R_f 0.32 (methanol/chloroform, 5:95); IR ($CHCl_3$) 3650, 3600, 2950, 1470, 1040 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.02 (d, $J = 7$ Hz, 3 H), 1.36–1.83 (m, 6 H), 1.83–1.94 (m, 1 H), 3.18 (dd, $J_1 = 9.0$, $J_2 = 3.0$ Hz, 1 H), 3.22 (br s, 2 H), 3.96 (dt, $J_1 = 5.0$, $J_2 = 3.0$ Hz, 1 H).

2(*R*)-Methylhexanedial (26a). To a solution of 1(*S*),2(*R*)-dihydroxy-3(*R*)-methylcyclohexane (**25a**) (227.5 mg, 1.75 mmol) in 10 mL of anhydrous THF, cooled to 0 °C, was added a solution of periodic acid (442 mg, 1.93 mmol) in 6 mL of THF. After 10 min, the reaction mixture was warmed to room temperature, and stirring was continued for 1 h. The reaction was then diluted with 20 mL of ether and washed with saturated sodium bicarbonate solution (10 mL) and brine (2 × 10 mL), and the organic layer was dried over sodium sulfate. The solvent was evaporated under reduced pressure to yield 207 mg (91%) of 2-(*R*)-methylhexanedial (**26a**) as a light yellow oil, which was used without purification: R_f 0.55 (hexane/ethyl acetate, 1:1); IR (neat) 2930, 2850, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, $J = 7.8$ Hz, 3 H), 1.35–1.46 (m, 1 H), 1.59–1.81 (m, 3 H), 2.31–2.42 (m, 1 H), 2.44–2.54 (td, $J_1 = 7.0$ Hz, $J_2 = 1.8$ Hz, 2 H), 9.63 (d, $J = 2$ Hz, 1 H), 9.83 (t, $J = 1.8$ Hz, 1 H).

2(*S*)-Methylhexanedial (26b). This compound was prepared via the same procedure used for **26a**: yield 86%; R_f 0.55 (hexane/ethyl acetate, 1:1); IR (neat) 2945, 2870, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, $J = 7.8$ Hz, 3 H), 1.35–1.40 (m, 1 H), 1.59–1.81 (m, 3 H), 2.31–2.42 (m, 1 H), 2.44–2.54 (td, $J_1 = 7.0$ Hz, $J_2 = 1.8$ Hz, 2 H), 9.63 (d, $J = 2$ Hz, 1 H), 9.83 (t, $J = 1.8$ Hz, 1 H).

3(*R*)-Methylcyclopentene-1-carboxaldehyde (7).[18] To a solution of 2(*R*)-methylhexanedial (**26a**) (155 mg, 1.21 mmol) in 15 mL of anhydrous ether at 0 °C was added dropwise freshly distilled piperidine (114.7 mg, 1.35 mmol). After 2.5 h at 0 °C, glacial acetic acid was added dropwise (324 mg, 5.40 mmol). The reaction mixture was warmed to room temperature, and stirring was continued for 3 h. The reaction was quenched with 10 mL of saturated sodium bicarbonate solution, the layers were separated, and the organic layer was washed with brine (2 × 5 mL) and dried over Na_2SO_4. The solvent was distilled off at atmospheric pressure, and the liquid residue was distilled (Kugelrohr 30 °C/2 mmHg) to yield 80 mg (0.73 mmol, 60%) of pure **7**: R_f 0.58 (silica gel, hexane/ethyl acetate, 8:2); $[\alpha]^{25}_D$ +193.3° (*c* 1.058 $CHCl_3$); IR (neat) 2960, 2870, 1680, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, $J = 8$ Hz, 3 H), 1.46–1.6 (m, 1 H), 2.19–2.31 (m, 1 H), 2.38–2.52 (m, 1 H), 2.52–2.66 (m, 1 H), 2.93–3.08 (m, 1 H), 6.77 (dd, $J_1 = 4.0$, $J_2 = 2.0$ Hz, 1 H), 9.8 (s, 1 H).

3(*S*)-Methylcyclopentene-1-carboxaldehyde (6).[18] The *S* enantiomer was prepared from 3(*S*)-methylhexanedial (**26b**) via the same procedure: yield 44.8%; R_f 0.58 (hexane/ethyl acetate, 8:2); $[\alpha]^{25}_D$ −214.9° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2980, 2890, 1675, 1605 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 1.13 (d, J = 8 Hz, 3 H), 1.42–1.56 (m, 1 H), 2.13–2.27 (m, 1 H), 2.33–2.50 (m, 1 H), 2.50–2.63 (m, 1 H), 2.87–3.04 (m, 1 H), 6.73 (dd, J_1 = 4.0, J_2 = 2.0 Hz, 1 H), 9.75 (s, 1 H).

2,8,8-Trimethyl-2,3-oxa-7,9-dioxalcyclo[4.3.0]non-4-ene (4a). To a mixture of **13**[3] (200 mg, 1.2 mmol) in 1,2-dichloroethane (8 mL) and borax buffer pH 8 (10 mL) was added MCPBA (80% purity, 250 mg, 1.2 mmol) at room temperature. The reaction was stirred overnight and then diluted with $CHCl_3$ (1 × 15 mL). The solution washed with saturated Na_2SO_3 (1 × 10 mL), saturated $NaHCO_3$ (1 × 10 mL), and H_2O (1 × 10 mL) and dried over Na_2SO_4, and solvent was evaporated to give crude **4a**. Column chromatography (10% deactivated silica, hexane/ethyl acetate, 90:10) gave 73 mg (40%) of pure **4a**: R_f 0.3 (hexane/ethyl acetate, 3:1); IR (neat) 3030, 2980, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 6 H), 1.50 (s, 3 H), 3.12 (d, J = 4 Hz, 1 H), 4.48 (s, 2 H), 5.68 (dd, J_1 = 10, J_2 = 2 Hz, 1 H), 5.94 (ddd, J_1 = 10, J_2 = 4, J_3 = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.4 (CH_3), 26.2 (CH_3), 27.9 (CH_3), 53.9 (CH), 72.4 (CH), 75.1 (CH), 110.1 (C), 123.3 (CH), 132.5 (CH); mass spectrum (70 eV), m/e (relative intensity) 167 (2), 156 (24), 139 (90), 111 (52), 73 (100); calcd for $C_9H_{11}O_3$ (M − 15) 167.0708, found 167.0681.

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Registry No. 1, 41977-20-2; **2b**, 114763-34-7; **4a**, 114763-41-6; **5**, 104010-72-2; **6**, 114818-65-4; **7**, 114818-64-3; **9**, 592-57-4; **10**, 1700-10-3; **12**, 114818-66-5; **13**, 114763-30-3; **14**, 4216-41-5; **15**, 105582-16-9; **17**, 114763-37-0; **18**, 114763-38-1; **19**, 638-37-9; **20**, 1072-21-5; **21**, 61031-76-3; **22a**, 114763-31-4; **22b**, 114763-35-8; **22c**, 114763-36-9; **23**, 114763-32-5; **24**, 114763-33-6; **25a**, 41977-21-3; **25b**, 41977-22-4; **26a**, 114763-39-2; **26b**, 114763-40-5; **28**, 65986-73-4; **29**, 114763-28-9; **30**, 114763-29-0; toluene, 108-88-3; chlorobenzene, 108-90-7; vinylbenzene, 100-42-5; phenylacetylene, 536-74-3.

Enantioselective Total Synthesis of (+)-12,13-Epoxytrichothec-9-ene and Its Antipode†,[1]

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Abstract: The 1,4-addition reactions of the anions derived from various cyclic allylic sulfoxides and 2-cyclopentenones were examined. Methyl substitution at C-3 of 2-cyclopentenones hinders the 1,4-addition. The activated enone, 2-(methoxycarbonyl)-3-methyl-2-cyclopentenone (**4**), however, afforded excellent chemical and optical yields of the 1,4-adducts. (+)-12,13-Epoxytrichothec-9-ene [(+)-**1**] and its antipode (−)-**1** were enantioselectively synthesized from (*S*)-(−)-4-methyl-2-cyclohexenone in 11 steps.

The intense interest in trichothecenes[3] stems from the fact that many of the trichothecenes, especially the macrocyclic trichothecene esters, exhibit a wide range of significant biological activities, including antibiotic, antifungal, and particularly antitumor properties. A variety of synthetic studies of trichothecenes has been reported;[4] however, only one deals with the synthesis of an optically active trichothecene, anguidine.[4a] As part of our continuing studies to utilize the enantioselective 1,4-addition reactions of chiral sulfinylallyl anions with cyclic enones,[5] the synthesis of the family of trichothecenes was undertaken. Herein, we report the full account of the first synthesis of optically pure (+)-12,13-epoxytrichothec-9-ene [(+)-**1**][6] and its antipode (−)-**1**.

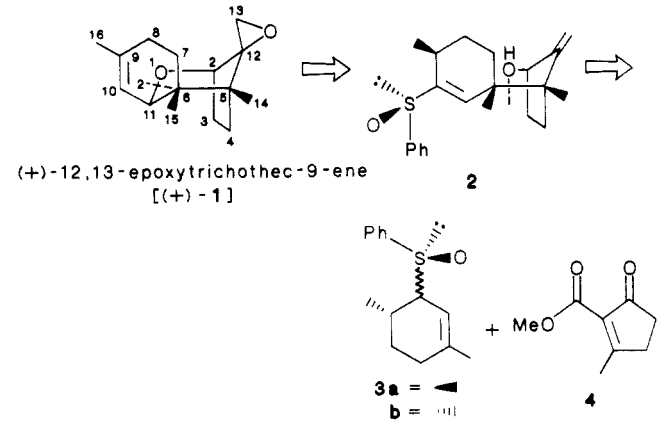
Results and Discussion

A convergent synthesis of the trichothecene skeleton is assembled from the addition of an A-ring unit to a C-ring unit followed by an intramolecular cyclization providing the B ring (Scheme I). We expect bond 1 in structure **2** could be formed via the conjugate addition of a *trans*-sulfinylallyl anion to an enone. Bond 2 would be contructed via the intramolecular Michael-type reaction of the hydroxyl and α,β-unsaturated sulfoxide moieties.[7]

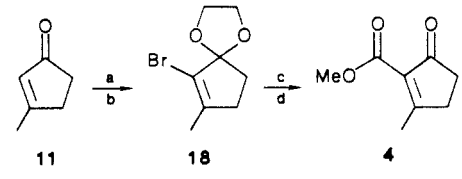
The scope of the 1,4-addition reactions of various racemic cyclic allylic sulfoxides and cyclopentenones was examined first. The results are summarized in Table I. The general procedure for these reactions consists in treating the sulfoxide with 1 equiv of lithium diisopropylamide (LDA) in THF at −78 °C for 1 h, and then treating this solution with 1 equiv of the cyclic enone at −78 °C. The relative stereochemistry is predicted from earlier results.[5,8,9]

Racemic sulfoxide **6** was prepared from 3-methyl-2-cyclohexen-1-ol in a two-stage reaction sequence: (i) tosylation with CH_3Li and *p*-toluenesulfonyl chloride (TsCl) followed by displacement with sodium benzenethiolate and (ii) oxidation of the resulting sulfide with 1 equiv of 30% H_2O_2 in acetic acid (AcOH).

Scheme I



Scheme II[a]



[a] (a) Br_2/Et_3N, CCl_4; (b) ethylene glycol, H^+; (c) *n*-BuLi, $ClCO_2Me$; (d) $(CO_2H)_2$, THF, H_2O.

† This paper is dedicated to E. J. Corey on the occasion of his 60th birthday.

(1) Part of this work is taken from the Ph.D. Dissertation of S. Venkataraman, Kansas State University.

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