

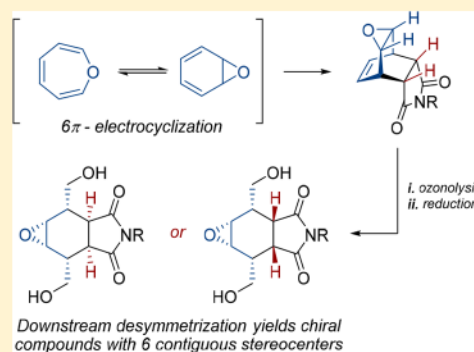
Synthesis and Desymmetrization of *meso* Tricyclic Systems Derived from Benzene Oxide

Desirée M. Matías and Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

S Supporting Information

ABSTRACT: Ozonolysis of the Diels–Alder adducts derived from benzene oxides and *N*-alkylmaleimides resulted in fully substituted, *meso* bicyclic systems bearing six contiguous stereocenters, isolated as diols upon reductive workup with NaBH₄. Variation in the workup allowed for isolation of two different diastereoisomers, through double epimerization of the imide stereocenters. Desymmetrization of the resulting *meso* diols via asymmetric nucleophilic epoxide opening and acylation reactions provided access to highly substituted, enantioenriched fused rings.



The synthesis of highly substituted, enantioenriched cyclohexanes is an ongoing challenge in organic synthesis.¹ Cyclohexadienes serve as versatile building blocks for the efficient synthesis of these molecules, and complex natural products and pharmaceuticals have benefited from their manipulation.² Specifically, functionalization of 1,2-disubstituted cyclohexadienes has allowed access to complex molecules with multiple stereocenters (Scheme 1a).³

1,2-Disubstituted cyclohexa-3,5-dienes are useful precursors for the synthesis of chiral, functionalized cyclohexanes.⁴ One type of 1,2-disubstituted cyclohexa-3,5-diene, benzene oxide, offers the potential of both diene and epoxide functionalization,

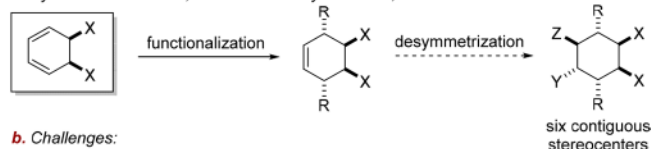
rendering it an attractive building block. Enzymatic oxidation of aromatic compounds has prompted a number of studies focused on the biosynthetic pathway and structural properties of arene oxides;^{5–7} however, the utility of these molecules as building blocks in organic synthesis has not been extensively researched. Epoxide opening⁸ (including one enantioselective case),^{8b} diene functionalization,⁹ and Diels–Alder reactivity¹⁰ have been reported with benzene oxide, but the scope of these transformations are limited or underexplored. This is most likely due to the rapid equilibrium that exists between benzene oxide and its valence-tautomer, oxepin, and the facile rearrangement of arene oxide to phenol by way of a 1,2-hydride shift and rearomatization promoted by acids or heat (Scheme 1b).¹¹

Nonetheless, benzene oxide derivatives offer interesting possibilities in the realm of desymmetrization chemistry. The desymmetrization of *meso* compounds has proven to be a powerful approach for the synthesis of chiral scaffolds bearing multiple stereocenters.¹² This strategy rapidly builds complexity by differentiating enantiotopic groups through the use of a chiral catalyst. A variety of transformations have been deployed in enantioselective desymmetrizations, including epoxide openings,¹³ alcohol functionalizations,¹⁴ and C–C bond formation¹⁵ of prochiral or *meso* compounds. We envisioned that symmetrical benzene oxide derived cycloadducts containing multiple contiguous stereocenters could be oxidatively cleaved and subsequently desymmetrized to access stereochemically dense molecules.

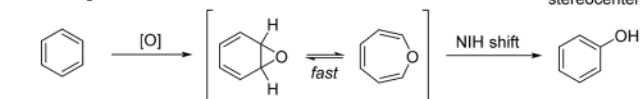
The direct oxidative dearomatization of aromatic feedstocks to arene oxide derivatives has primarily been accomplished via

Scheme 1. Synthesis of *meso* Compounds Derived from Aromatic Molecules and Challenges Associated with Benzene Oxide

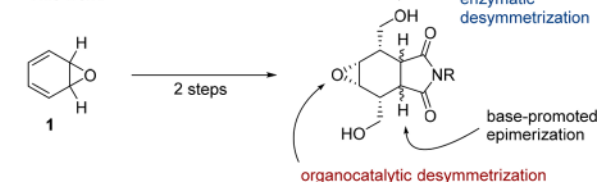
a. Cyclohexanes from 1,2-disubstituted cyclohexa-3,5-dienes



b. Challenges:



c. This work:



Received: February 26, 2018

Table 1. Synthesis of *meso* Bicyclic Compounds from Benzene Oxides 1 and 2

1, R = H
2, R = CH₂CH₂CH₂

solvent, rt, time

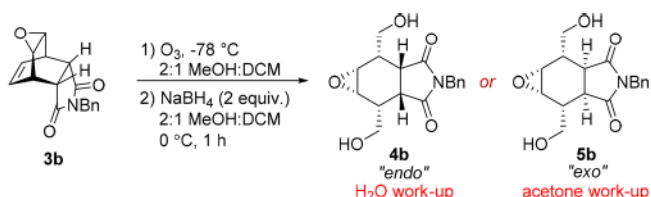
3

entry	product	R	X	Y	solvent	time (h)	yield (%)
1	3a	H	O	CH	Et ₂ O	72	71
2	3b	H	NBn	CH	Et ₂ O	24	50
3	3c	H	NPh	CH	Et ₂ O	24	53
4	3d	H	NC ₈ H ₁₇	CH	Et ₂ O	72	61
5	3e	H	NPh	N	acetone	1	65
6	3f	CH ₂ CH ₂ CH ₂	NBn	CH	Et ₂ O	24	57

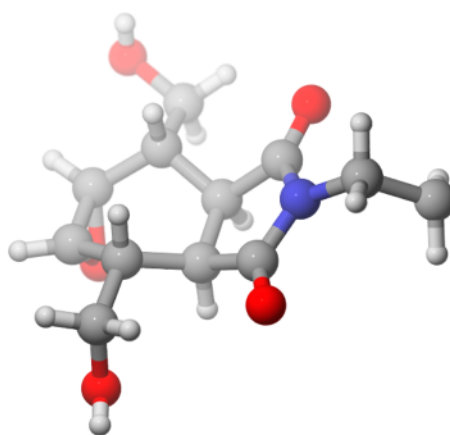
enzymatic pathways, but in most cases, the presence of electron-withdrawing groups is needed in order to isolate the desired oxides and prevent rearomatization.¹⁶ Nonenzymatic pathways have been limited by low yields and operational practicality.¹⁷ To date, an efficient, dearomative, nonenzymatic synthesis of benzene oxide has not been reported. As part of a long-term goal of utilizing aromatic feedstocks for the creation of chiral compounds, we sought to explore the reactivity of benzene oxide. Herein, we present stage one of this investigation, the synthesis of new, chiral, fully substituted cyclohexanes using benzene oxide as the starting building block (Scheme 1c).

Benzene oxide can be chemically accessed in a stepwise fashion, starting from commercially available 1,4-cyclohexadiene. This method, developed initially by Günther, has allowed access to benzene oxide for mechanistic and kinetic studies.^{11,10b} We modified this procedure in order to obtain an operationally simple route that does not require heat or purification (Experimental Section). From this point, *meso* tetracycles 3a–3f were accessed from the Diels–Alder reaction of benzene oxide with maleic anhydride and a number of *N*-substituted maleimides (Table 1). These *meso* compounds bearing six contiguous stereocenters have not been employed in organic synthesis prior to this study; conformational studies have been performed with 3c.^{10b} The bicyclic products 3a, 3b, and 3e have been previously synthesized by Günther,¹¹ Gillard,^{10b} and Golding,^{10d} respectively. The *N*-benzyl maleimide adduct 3c (entry 3) was synthesized in 53% yield, and *N*-octyl maleimide adduct 3d (entry 4) was obtained in 61% yield. Furthermore, the indane derived tricyclic compound 3f (entry 6) could be afforded in 57% yield. At this point, an oxidative cleavage reaction was employed to access substituted *meso* fused cyclohexanes with six contiguous stereocenters.

Ozonolysis of anhydride 3a resulted in a mixture of starting material and decomposition as the compound was highly insoluble under the reaction conditions. Fortunately, Diels–Alder adduct 3b was tolerant of the reaction conditions, providing diol 4b in 98% yield after a NaBH₄ workup (Scheme 2). Using Me₂S for the workup conditions rendered a labile putative dialdehyde that decomposed readily. Unexpectedly, the conditions by which the NaBH₄ was quenched had an effect in the stereoselectivity of the reaction. Addition of water to quench the remaining NaBH₄ resulted in the expected *endo* product 4b; however, if acetone was added instead and the solution was concentrated and allowed to stir overnight, the thermodynamically favored *exo* product 5b was obtained in a 9:1 dr.

Scheme 2. Ozonolysis Reaction of *meso* Compound 3b and the Effect of Quenching Conditions on the Diastereoselectivity

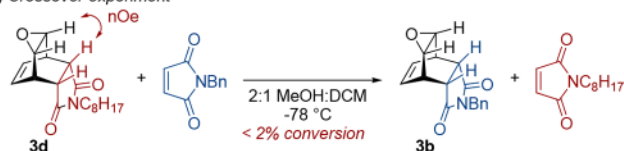
To elucidate the identity of the diastereoisomers, an X-ray crystallography study of the related diol 5d was performed, revealing a *syn*-relationship between the epoxide and the α -protons, characteristic of having arisen from the *exo* Diels–Alder adduct (Figure 1).¹⁸

Figure 1. X-ray structure of succinimide 5d. The *n*-octyl chain was truncated for better visualization.

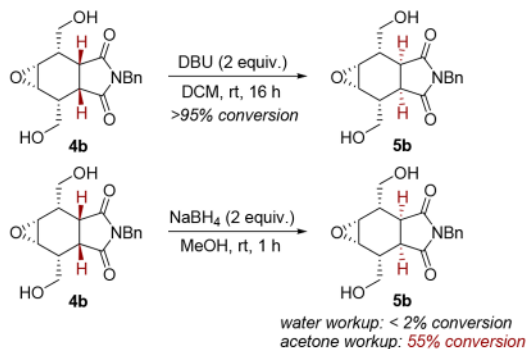
In contrast, an NOE correlation was observed between the epoxide C–H methine and the proximal succinimide C–H methine in cycloadduct 3d, thus showing that the initial Diels–Alder adduct is *endo* selective. In order to rule out an unlikely retro-Diels–Alder/Diels–Alder pathway where the *exo* Diels–Alder adduct would be trapped at the lower temperatures required by the ozonolysis reaction, we performed a crossover experiment using *N*-octyl adduct 3d and *N*-benzyl maleimide; however, as expected, only *N*-octyl maleimide adduct 3d was observed, ruling out the retro-Diels–Alder pathway (Scheme 3a).

Scheme 3. Experiments Probing the Mechanism of Diastereomerization

(a) Crossover experiment



(b) Base-promoted isomerization



Alternatively, we considered the possibility that the *exo* product 5b could form directly from *endo* diol 4b through a double epimerization pathway. Addition of DBU to 4b resulted in complete conversion to 5b after 16 h (Scheme 3b). Double epimerization reactions of *N*-substituted maleimides are unusual;¹⁹ it is possible that the presence of the diol increases the acidity of the α -protons via formation of a hydrogen bond with the carbonyl oxygen. To ensure that a double epimerization was occurring under our ozonolysis conditions with the acetone workup, we subjected the *endo* diol 4b to the reductive conditions and aqueous or acetone workups. Using the aqueous workup, only the *endo* diol 4b was observed, whereas the acetone workup provided the *exo* diol 5b with 55% conversion after only 1 h. Thus, addition of acetone in the presence of NaBH_4 results in the formation of a base sufficiently potent to promote the double epimerization reaction.

We next sought to expand the scope of the oxidative cleavage (Figure 2). Ozonolysis of the *N*-phenyl adduct 3c using the aqueous workup resulted in 46% yield of the *endo* product 4c; however, application of the acetone workup proved difficult and resulted mainly in an inseparable mixture of products. Pleasingly, when utilizing the *N*-octyl adduct 3d, both the *endo* and *exo* products could be obtained. While *endo* product 4d was obtained selectively, the corresponding *exo* diol 5d was obtained in a 1.4:1 dr; the diastereoselectivity could be improved to >20:1 if the diol was stirred with DBU overnight. Using the adduct derived from the indane benzene oxide 3f, both diols were obtained selectively; the *exo* diol 5f was obtained directly from the acetone workup and did not require further manipulation. Finally, ozonolysis of the tetracyclic dihydrotriazolopyridazinedione 3e resulted in the derived diol 4e in 65% yield. These products are sensitive to silica gel; a reduction in diastereoselectivity was observed in various cases after column chromatography (Experimental Section).

With these *meso* diols in hand, we sought to carry out initial explorations of desymmetrizing transformations that would provide access to fully substituted, chiral cyclohexanes with six contiguous stereocenters. The use of a chiral phosphoric acid catalyst and 2-mercaptotiazole resulted in the opening of the epoxide 4d, providing alcohol 6 in 63% yield and 90:10 er

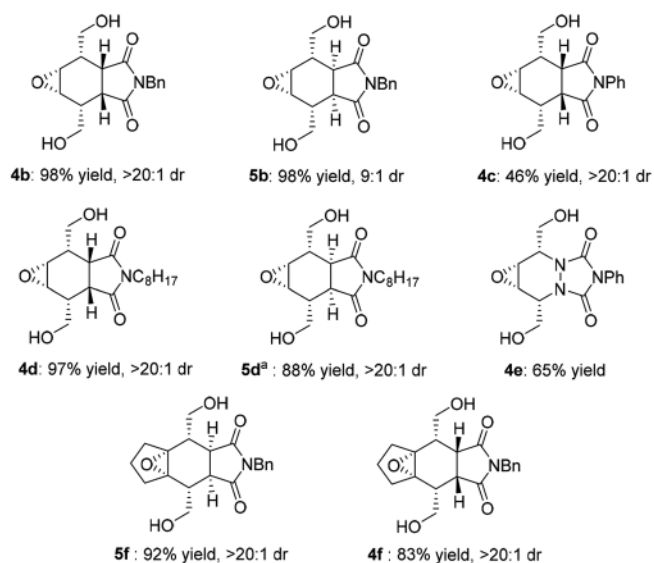
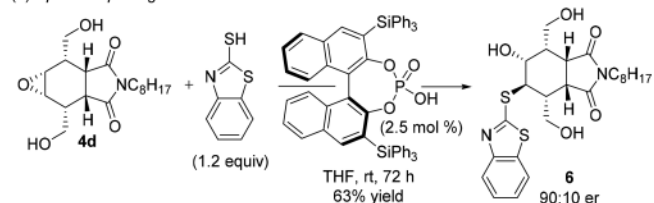


Figure 2. Scope of the ozonolysis reaction of *meso* bicyclic compounds. Footnote a represents the compound after DBU stir.

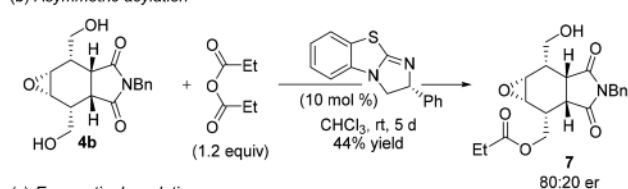
(Scheme 4a).²⁰ Employing the opposite imide diastereoisomer (5d) or changing the *N*-substituent resulted in lower

Scheme 4. Enantioselective Desymmetrization of *meso* Products

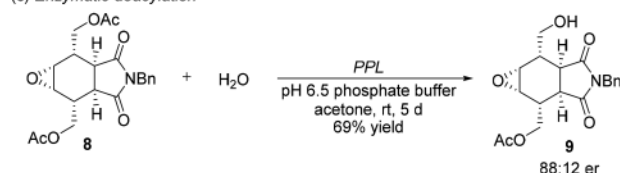
(a) Epoxide opening



(b) Asymmetric acylation



(c) Enzymatic deacylation



enantiomeric ratios. Enantioselective diol monofunctionalization could be achieved using Birman's acylation catalyst and propionic anhydride.²¹ The *endo* diol 4b was monoacylated to obtain propionate 7 in 44% yield and 80:20 er. Finally, subjecting the *meso* diacetate 8 to enzymatic deacylating conditions using porcine pancreatic lipase yielded monoacetate 9 in 69% yield and 88:12 er.^{22,23}

In conclusion, we have disclosed the synthesis of *meso* diols derived from the benzene oxide/oxepin equilibrium. These compounds have not been previously accessed through other synthetic methods, and similar compounds are still challenging to obtain. Fully substituted chiral compounds were acquired

through desymmetrizing epoxide opening and acylation reactions. This work provides further support to the notion that the synthesis of complex, chiral molecules can be achieved using benzene oxide as a building block.

EXPERIMENTAL SECTION

General Comments. Nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR, ^{19}F NMR) were recorded at the following frequencies: ^1H NMR at 400 or 600 MHz, ^{13}C NMR at 101 or 151 MHz with solvent resonance as the internal standard (^1H NMR CDCl_3 at 7.26 ppm and ^{13}C NMR CDCl_3 at 77.0 ppm). ^1H NMR data are reported as follows: chemical shift, multiplicity (abbreviations s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, qt = quintet, and m = multiplet), coupling constant (Hz), and integration. High resolution mass spectra were obtained using a linear trap quadrupole Fourier transform (LTQ-FT) spectrometer. TLC visualization was accomplished using UV light, phosphomolybdic acid in ethanol, or an aqueous ceric ammonium nitrate solution. High performance liquid chromatography (HPLC) analyses were carried out using Diacel Chiralpak IA and IC columns. Samples were prepared using 90:10 HPLC grade *i*PrOH/hexanes and eluted with HPLC grade hexanes with the indicated percentage of *i*PrOH with an oven temperature of 40 °C. Yields and diastereomeric ratios (dr's) are reported herein for a specific experiment and as a result may differ slightly from those found in the schemes, which are averages of at least two experiments. Nitrogen was dried by passage through anhydrous calcium sulfate with 3% cobalt chloride as an indicator. *N*-Benzylmaleimide,²⁴ *N*-octylmaleimide,²⁵ *N*-phenylmaleimide,²⁶ and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)²⁷ were prepared according to known literature procedures. Birman's catalyst²¹ and the phosphoric acid catalyst (TiPSY)²⁸ were prepared according to known literature procedures. The benzene oxides were prepared by modifying a literature procedure.^{10b} All other reagents and solvents were purchased from commercial sources and used as received.

Modified Procedure for the Synthesis of 3,4-Dibromo-7-oxabicyclo[4.1.0]heptane. A solution of Br_2 (2.05 mL, 40 mmol) in hexanes (20 mL) was added dropwise to a solution of 1,4-cyclohexadiene (3.78 mL, 40 mmol) in hexanes (45 mL) that had been cooled to -45 °C using a dry ice/acetonitrile bath. (Note that the reaction turns yellow upon addition of bromine and should not be allowed to turn completely orange; lower yields resulted when this occurred.) After the addition was complete, the yellow solution was allowed to reach room temperature and then filtered. The solution was concentrated under reduced pressure. The resulting oil solidified upon cooling, and it was dissolved in dichloromethane (20 mL). This solution was added to a solution of *m*CPBA (13.4 g, 58 mmol) in dichloromethane (330 mL) at room temperature. The reaction was allowed to stir at that temperature for 72 h. A 20% aq solution of $\text{Na}_2\text{S}_2\text{O}_5$ (100 mL) was added, and the solution was allowed to stir for 20 min. The layers were then separated, and the organic layer was washed with a saturated aq NaHCO_3 solution (2 $\times$ 100 mL) and brine (100 mL $\times$ 1). The organic layer was dried with sodium sulfate, filtered, and concentrated under a vacuum to yield the clean product as an off white crystalline solid (6.85 g, 26.8 mmol, 68% yield over two steps). The product was carried on to the next step without further purification. Spectroscopic data was identical to those previously reported:^{10b} ^1H NMR (400 MHz, CDCl_3) δ 4.30 (td, J = 7.1, 4.6 Hz, 1H), 4.19 (q, J = 6.7 Hz, 1H), 3.17 (m, 2H), 3.00 (dd, J = 16.0, 4.6 Hz, 1H), 2.90 (ddd, J = 16.5, 6.4, 3.6 Hz, 1H), 2.65 (dd, J = 16.6, 6.3 Hz, 1H), 2.46 (ddd, J = 16.1, 6.7, 3.4 Hz, 1H).

Synthesis of 5,6-Dibromohexahydro-1H-3a,7a-epoxyindene. A solution of Br_2 (0.19 mL, 3.67 mmol) in dichloromethane (6 mL) was added over a period of 30 min to a solution of 2,3,4,7-tetrahydro-1H-3a,7a-epoxyindene⁹ (1.0 g, 3.67 mmol) in dichloromethane (30 mL) cooled to -78 °C. The addition was stopped when the orange color persisted. (Note that the bromine solution was not added completely.) The reaction was allowed to reach room

temperature, and the solution was concentrated under reduced pressure to yield a yellow oil. The oil was crystallized from pentanes at -20 °C to obtain the product as clear crystals (722 mg, 2.44 mmol, 66% yield). Spectroscopic data was identical to those previously reported:^{10b} ^1H NMR (400 MHz, CDCl_3) δ 4.41 (q, J = 5.4 Hz, 1H), 4.29 (q, J = 5.9 Hz, 1H), 3.01 (dd, J = 15.9, 4.4 Hz, 1H), 2.82 (dd, J = 16.4, 6.3 Hz, 1H), 2.68 (dd, J = 16.4, 4.9 Hz, 1H), 2.42 (dd, J = 15.9, 5.4 Hz, 1H), 2.05 (dt, J = 12.4, 8.9 Hz, 2H), 1.55 (m, 4H).

General Procedure A for the Preparation of Diels–Alder Adducts (3a–3d). *Benzene Oxide/Oxepin.* DBU (4 equiv) was added to a solution of 3,4-dibromo-7-oxabicyclo[4.1.0]heptane (1 equiv) in Et_2O (10 mL) at room temperature. The reaction was allowed to stir for 24 h at that temperature and then a saturated aq solution of NaHCO_3 was added until all of the precipitate was dissolved. The layers were separated, and the aqueous layer was extracted with Et_2O (3 $\times$ 5 mL). The organic layers were combined and washed with brine. (Note that, if the organics are not washed with brine, lower yields result in Diels–Alder reactions.) The organic extracts were dried with sodium sulfate, filtered, and concentrated under a stream of air. The yellow liquid was used immediately to avoid decomposition. The same procedure was used for the substituted benzene oxide, where $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_2$.

The crude benzene oxide/oxepin was redissolved in approximately 10 mL of ether, and the dienophile (1 equiv) was added as a solid. The reaction was allowed to stir at room temperature for the required time. The resulting precipitate was collected and washed with cold ether. Only products 3d and 3f required further purification.

1a,2,2a,5a,6,6a-Hexahydro-2,6-ethenooxireno[2,3-f]-isobenzofuran-3,5-dione (3a). The title compound was prepared according to general procedure A using benzene oxide (7.8 mmol), maleic anhydride (766 mg, 7.8 mmol), and Et_2O (20 mL) and was stirred for 72 h. The product was obtained as a white powder (1.06 g, 7.81 mmol, 71% yield). Spectroscopic data were identical to those previously reported:¹¹ ^1H NMR (400 MHz, CDCl_3) δ 5.97 (dd, J = 4.7, 3.5 Hz, 2H), 3.73–3.66 (m, 2H), 3.40 (dd, J = 4.0, 2.2 Hz, 2H), 3.27 (t, 1.8 Hz, 2H).

4-Benzyl-1a,2,2a,5a,6,6a-hexahydro-3H-2,6-ethenooxireno[2,3-f]isoindole-3,5(4H)-dione (3b). The title compound was prepared according to general procedure A using benzene oxide (4.12 mmol), benzyl maleimide (771 mg, 4.12 mmol), and Et_2O (10 mL) and was stirred for 24 h. The product was obtained as a white powder (263 mg, 0.935 mmol, 48% yield). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.24 (m, 5H), 5.71 (dd, J = 4.8, 3.4 Hz, 2H), 4.57 (s, 2H), 3.65–3.57 (m, 2H), 3.40–3.35 (m, 2H), 2.97 (t, J = 1.8 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 176.7, 137.1, 123.3, 48.6, 31.1. IR (thin film, cm^{-1}): 3433, 1769, 1698, 1396, 1266, 1173, 1054. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{Na}$, 304.0944; found, 304.0947. Mp: 180–185 °C.

4-Phenyl-1a,2,2a,5a,6,6a-hexahydro-3H-2,6-ethenooxireno[2,3-f]isoindole-3,5(4H)-dione (3c). The title compound was prepared according to general procedure A using benzene oxide (4.12 mmol), phenyl maleimide (771 mg, 4.12 mmol), and Et_2O (10 mL) and was stirred for 24 h. The product was obtained as a white powder (277 mg, 1.04 mmol, 53% yield). Spectroscopic data were identical to those previously reported:^{10b} ^1H NMR (400 MHz, CDCl_3) δ 7.48–7.35 (m, 3H), 7.19–7.11 (m, 2H), 5.95 (dd, J = 4.7, 3.4 Hz, 2H), 3.76–3.66 (m, 2H), 3.47–3.39 (m, 2H), 3.13 (t, J = 1.8 Hz, 2H).

4-Octyl-1a,2,2a,5a,6,6a-hexahydro-3H-2,6-ethenooxireno[2,3-f]isoindole-3,5(4H)-dione (3d). The title compound was prepared according to general procedure A using benzene oxide (4.12 mmol), octyl maleimide (771 mg, 4.12 mmol), and Et_2O (10 mL) and was stirred for 72 h. The solution was concentrated, and the crude was purified using column chromatography with hexanes/ethyl acetate (gradient, 5:1 to 1:1) to yield the product as a white solid (380 mg, 1.25 mmol, 64% yield). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 5.80 (dd, J = 4.7, 3.4 Hz, 2H), 3.66–3.55 (m, 2H), 3.43–3.32 (m, 4H), 2.93 (t, J = 1.8 Hz, 2H), 1.50–1.39 (m, 2H), 1.32–1.15 (m, 10H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.1, 126.6, 47.4, 42.0, 38.8, 35.5, 31.7, 29.1, 27.6, 26.7, 22.6, 14.1. IR (thin film, cm^{-1}): 2928, 2855, 1772, 1698, 1402, 1266, 1171. HRMS (ESI-

TOF) m/z : $[M + H]^+$ calcd for $C_{18}H_{26}NO_3$, 304.1907; found, 304.1912. Mp: 110–114 °C. TLC (1:1 hexanes/ethyl acetate): R_f = 0.4.

5-Phenyl-1a,2,8,8a-tetrahydro-4H-2,8-ethenooxireno[2,3-d]-[1,2,4]triazolo[1,2-a]pyridazine-4,6(5H)-dione (3e). The title compound was made according to a literature procedure^{10d} using benzene oxide (1.95 mmol) and 4-phenyl-1,2,4-triazole-3,5-dione (171 mg, 0.977 mmol). The product was purified using column chromatography with 1:1 hexanes/ethyl acetate to obtain 3e as a white solid (171 mg, 0.635 mmol, 65% yield). Spectroscopic data were identical to those previously reported:^{10d} 1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.29 (m, 5H), 6.17 (t, J = 3.8 Hz, 2H), 5.31 (d, J = 3.9 Hz, 2H), 3.79–3.61 (m, 2H).

2-Benzyl-3a,4,6,7,8,8a-hexahydro-1H,5H-4a,7a-epoxy-4,8-ethenocyclopenta[*f*]isoindole-1,3(2H)-dione (3f). The title compound was prepared according to general procedure A using 2,3-dihydro-1H-3a,7a-epoxyindene (1.69 mmol), benzyl maleimide (316 mg, 1.69 mmol), and Et_2O (8.5 mL) and stirred for 24 h. The solution was concentrated, and the crude was purified using column chromatography with hexanes/ethyl acetate (gradient, 5:1 to 1:1) to yield the product as a white solid (331 mg, 1.03 mmol, 61% yield). Analytical data: 1H NMR (600 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5H), 5.76 (dd, J = 4.7, 3.2 Hz, 2H), 4.56 (s, 2H), 3.58–3.44 (m, 2H), 3.08–3.01 (m, 2H), 2.02–1.95 (m, 2H), 1.86–1.78 (m, 1H), 1.75–1.67 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 135.5, 128.6, 128.5, 127.8, 64.3, 42.4, 42.3, 37.2, 25.4, 25.1. IR (thin film, cm^{-1}): 2953, 1699, 1396, 1340, 1174, 916. HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{20}H_{19}NO_3Na$, 344.1257; found, 344.1265. Mp: 179–181 °C. TLC (1:1 hexanes/ethyl acetate): R_f = 0.4.

General Procedure B for the Preparation of Diols (4a–4f). The Diels–Alder adduct (1 equiv) was dissolved in a 2:1 mixture of DCM/MeOH (0.11 M) and cooled to –78 °C in a dry ice/acetone bath. Ozone was bubbled through the solution until the reaction turned light blue, at which point the ozone bubbling was stopped, and the solution was sparged with nitrogen to purge excess ozone. Solid $NaBH_4$ (2 equiv) was added, and the reaction was moved to an ice bath. The reaction was allowed to stir for 1 h, and then 1 mL of water was added. The layers were separated, and the aqueous layer was extracted with DCM (2 mL $\times$ 3). The organic extracts were combined and dried with sodium sulfate, filtered, and concentrated to obtain the desired diol.

General Procedure C for the Preparation of Diols (5a–5f). The Diels–Alder adduct (1 equiv) was dissolved in a 2:1 mixture of DCM/MeOH (0.11 M) and cooled to –78 °C in a dry ice/acetone bath. Ozone was bubbled through the solution until the reaction turned light blue, at which point the ozone bubbling was stopped, and the solution was purged with nitrogen to get rid of excess ozone. Solid $NaBH_4$ (2 equiv) was added, and the reaction was moved to an ice bath. After stirring for 1 h, 1 mL of acetone was added and the reaction was stirred for 5 min. The solvent was removed in vacuo, and the residue was stirred overnight. Water (1 mL) and $EtOAc$ (1 mL) were then added, and the layers were separated. The aqueous layer was extracted with $EtOAc$ (3 $\times$ 2 mL), and the organics were combined, dried with sodium sulfate, and concentrated to yield the crude diol.

(1R,2S,5R,6R,6S)-4-Benzyl-2,6-bis(hydroxymethyl)hexahydro-3H-oxireno[2,3-*f*]isoindole-3,5(4H)-dione (4b). The title compound was prepared according to general procedure B using 3b (50 mg, 0.18 mmol), $NaBH_4$ (13.4 mg, 0.36 mmol), and 2:1 DCM/MeOH (1.5 mL) and was obtained as a clear amorphous solid (56 mg, 0.18 mmol, >98% yield, >20:1 dr). Analytical data: 1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J = 7.1 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.29–7.25 (m, 1H), 4.66 (s, 2H), 4.07 (dd, J = 11.9, 9.3 Hz, 2H), 3.97 (dd, J = 11.9, 5.5 Hz, 2H), 3.12 (s, 2H), 3.11–3.07 (m, 2H), 2.66–2.59 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.2, 138.6, 121.6, 64.1, 32.9. IR (thin film, cm^{-1}): 3417, 2939, 2885, 1769, 1683, 1405, 1186, 1029. HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{17}H_{20}NO_3$, 318.1336; found, 318.1333.

(1aR,2S,2aR,5aS,6R,6aS)-4-Benzyl-2,6-bis(hydroxymethyl)-hexahydro-3H-oxireno[2,3-*f*]isoindole-3,5(4H)-dione (5b). The title compound was prepared according to general procedure C using 3b

(50 mg, 0.18 mmol), $NaBH_4$ (13.4 mg, 0.36 mmol), and 2:1 DCM/MeOH (1.5 mL) and was obtained as a white solid (55 mg, 0.17 mmol, 98% yield, 9:1 dr). Analytical data: 1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.65 (s, 2H), 4.15–4.05 (m, 2H), 4.04–3.95 (m, 2H), 3.29 (s, 2H), 2.94–2.85 (m, 2H), 2.85–2.78 (m, 2H), 2.30–2.20 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.6, 135.2, 128.8, 128.6, 128.2, 65.2, 51.6, 42.6, 38.6, 37.1. IR (thin film, cm^{-1}): 3420, 1697, 1558, 1402, 1340, 1175, 1030. HRMS (ES-TOF) m/z : $[M + H]^+$ calcd for $C_{17}H_{20}NO_3$, 318.1336; found, 318.1334. Mp: 96–98 °C.

(1aR,2S,2aS,5aR,6R,6aS)-2,6-Bis(hydroxymethyl)-4-phenylhexahydro-3H-oxireno[2,3-*f*]isoindole-3,5(4H)-dione (4c). The title compound was prepared according to general procedure B using 3c (50.0 mg, 0.19 mmol), $NaBH_4$ (14.2 mg, 0.37 mmol), and 2:1 DCM/MeOH (1.5 mL) and was obtained as a white amorphous solid (42 mg, 0.14 mmol, 74% yield, >20:1 dr). Analytical data: 1H NMR (600 MHz, $CDCl_3$) δ 7.52–7.47 (m, 2H), 7.45–7.41 (m, 1H), 7.30–7.27 (m, 2H), 4.15 (dd, J = 11.9, 9.4 Hz, 2H), 4.03 (dd, J = 11.9, 5.6 Hz, 2H), 3.31–3.26 (m, 2H), 3.22 (s, 2H), 2.76–2.70 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.7, 129.3, 129.0, 126.7, 52.4, 39.2, 37.7. IR (thin film, cm^{-1}): 3446, 1698, 1497, 1396, 1201, 1042. HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{16}H_{17}NO_3Na$, 326.0999; found, 326.0990.

(1R,2S,5R,6R,6S)-2,6-Bis(hydroxymethyl)-4-octylhexahydro-3H-oxireno[2,3-*f*]isoindole-3,5(4H)-dione (4d). The title compound was prepared according to general procedure B using 3d (50 mg, 0.17 mmol), $NaBH_4$ (12.5 mg, 0.33 mmol), and 2:1 DCM/MeOH (1.5 mL) and was obtained as a white solid (53 mg, 0.16 mmol, 95% yield). Analytical data: 1H NMR (400 MHz, $CDCl_3$) δ 4.13–4.02 (m, 2H), 4.02–3.92 (m, 2H), 3.60–3.50 (m, 2H), 3.47 (t, J = 7.4 Hz, 2H), 3.12 (s, 2H), 3.09–3.00 (m, 2H), 2.67–2.54 (m, 2H), 1.62–1.47 (m, 2H), 1.35–1.16 (m, 10H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.6, 62.7, 52.2, 39.0, 37.3, 31.7, 29.1, 29.0, 27.1, 26.7, 22.5, 14.1. IR (thin film, cm^{-1}): 3420 (b), 2927, 2856, 1684, 1439, 1353, 1034. HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{18}H_{29}NO_3Na$, 362.1938; found, 362.1938. Mp: 65–69 °C.

(1aR,2S,2aR,5aS,6R,6aS)-2,6-Bis(hydroxymethyl)-4-octylhexahydro-3H-oxireno[2,3-*f*]isoindole-3,5(4H)-dione (5d). The title compound was prepared according to general procedure C using 3d (50 mg, 0.17 mmol), $NaBH_4$ (12.5 mg, 0.33 mmol), and 2:1 DCM/MeOH (1.5 mL) and was obtained with a 1.4:1 dr. To obtain the product in >20:1 dr, a DCM (0.7 mL) solution of the diastereomeric mixture was stirred with DBU (44 μ L, 0.29 mmol) at room temperature for 16 h. A saturated aq $NaHCO_3$ solution (2 mL) was added, and the layers were separated. The aqueous layer was extracted with DCM (3 $\times$ 2 mL), and the organics were combined, dried with sodium sulfate, and concentrated to afford the product as a white solid (47 mg, 0.14 mmol, 97% yield). Analytical data: 1H NMR (400 MHz, $CDCl_3$) δ 4.15–4.06 (m, 2H), 4.06–3.94 (m, 2H), 3.49 (t, J = 11.3 Hz, 2H), 3.30 (s, 2H), 2.99–2.81 (m, 4H), 2.32–2.19 (m, 2H), 1.71–1.47 (m, 3H), 1.34–1.16 (m, 10H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.0, 65.4, 65.4, 51.6, 39.1, 38.7, 38.7, 37.2, 31.7, 29.1, 29.0, 27.5, 26.7, 22.6, 14.1. IR (thin film, cm^{-1}): 3420 (b), 2926, 2856, 1769, 1694, 1406, 1065. HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{18}H_{30}NO_3$, 340.2118; found, 340.2111. Mp: 78–81 °C.

(1aR,2S,8R,8aS)-2,8-Bis(hydroxymethyl)-5-phenyltetrahydro-4H-oxireno[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-4,6(5H)-dione (4e). The title compound was prepared according to general procedure B using 3e (50 mg, 0.19 mmol), $NaBH_4$ (14.1 mg, 0.37 mmol), and 2:1 DCM/MeOH (1.5 mL). The product was purified using silica gel column chromatography with DCM/MeOH 20:1 and was obtained as a white solid (34.0 mg, 0.11 mmol, 60% yield). Analytical data: 1H NMR (600 MHz, $CDCl_3$) δ 7.51–7.44 (m, 4H), 7.43–7.39 (m, 1H), 4.32–4.26 (m, 2H), 4.20–4.08 (m, 4H), 3.64 (dd, J = 2.3, 1.0 Hz, 2H), 3.49 (dd, J = 9.4, 4.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.4, 130.4, 129.3, 128.8, 125.7, 61.5, 55.9, 51.4. IR (thin film, cm^{-1}): 3419, 2894, 1769, 1698, 1430, 1292, 1077, 768. HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{14}H_{15}N_3O_3Na$, 328.0904; found, 328.0893. Mp: 119–122 °C. TLC (20:1 DCM/MeOH): R_f = 0.2.

(3*R*,4*R*,4*S*,7*R*,8*S*,8*S*)-2-Benzyl-4,8-bis(hydroxymethyl)hexahydro-1*H*,5*H*-4*a*,7*a*-epoxycyclopenta[*f*]isoindole-1,3(2*H*)-dione (**4f**). The title compound was prepared according to general procedure B using **3f** (50 mg, 0.16 mmol), NaBH₄ (11.8 mg, 0.31 mmol), and 2:1 DCM/MeOH (1.5 mL). The crude was purified using column chromatography with DCM/MeOH 20:1 and was obtained as a white amorphous solid (53 mg, 0.15 mmol, 95% yield). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.38–7.33 (m, 2H), 7.33–7.29 (m, 2H), 7.29–7.27 (m, 1H), 4.67 (s, 2H), 4.09 (ddd, *J* = 12.0, 9.8, 6.8 Hz, 2H), 3.98 (ddd, *J* = 12.3, 7.9, 4.8 Hz, 2H), 3.58 (dd, *J* = 7.9, 6.9 Hz, 2H), 3.20–3.14 (m, 2H), 2.66–2.59 (m, 2H), 2.11–2.02 (m, 2H), 1.63–1.53 (m, 4H), 1.36–1.27 (m, 1H); ¹³C NMR (150 MHz, CDCl₃): 179.6, 135.3, 128.6, 128.4, 127.9, 66.6, 61.6, 42.7, 40.2, 39.3, 28.2, 19.5. IR (thin film, cm⁻¹): 3446, 2952, 1685, 1431, 1350, 1169, 1054. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₀H₂₃NO₅Na, 380.1468; found, 380.1467. TLC (20:1 DCM/MeOH): *R*_f = 0.3.

(3*aR*,4*S*,4*aR*,7*aS*,8*R*,8*aS*)-2-Benzyl-4,8-bis(hydroxymethyl)-hexahydro-1*H*,5*H*-4*a*,7*a*-epoxycyclopenta[*f*]isoindole-1,3(2*H*)-dione (**5f**). The title compound was prepared according to general procedure C using **3f** (50 mg, 0.16 mmol), NaBH₄ (11.8 mg, 0.31 mmol), and 2:1 DCM/MeOH (1.5 mL) and was obtained as a light pink solid (51.6 mg, 0.14 mmol, 93% yield). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.26 (m, 5H), 4.65 (s, 2H), 4.16–4.07 (m, 2H), 3.96 (dd, *J* = 11.1, 5.9 Hz, 2H), 3.14–3.07 (m, 2H), 2.91–2.83 (m, 2H), 2.29–2.23 (m, 2H), 2.18–2.11 (m, 2H), 1.67–1.55 (m, 5H), 1.46–1.36 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 180.0, 135.3, 128.8, 128.7, 128.2, 66.2, 63.9, 42.6, 40.3, 39.0, 29.1, 19.5. IR (thin film, cm⁻¹): 3445, 2953, 1696, 1430, 1174, 1071, 733. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₀H₂₃NO₅Na, 380.1468; found, 380.1488. Mp: 151–155 °C.

Procedure for the Preparation of 6. Under an inert atmosphere, **4d** (17.0 mg, 0.05 mmol), the phosphoric acid (1.1 mg, 0.0012 mmol), and 2-mercaptobenzothiazole (10.0 mg, 0.06 mmol) were dissolved in anhydrous tetrahydrofuran (0.1 mL), and the mixture was stirred at room temperature for 72 h. The reaction was stopped by removal of the solvent under reduced pressure. Purification with column chromatography using 40:1 to 20:1 DCM/MeOH yielded **6** as a clear oil (16.0 mg, 0.032 mmol, 63% yield, 90:10 er). The absolute configuration is unassigned. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.78–7.70 (m, 2H), 7.43–7.36 (m, 1H), 7.34–7.27 (m, 1H), 4.24 (d, *J* = 2.7 Hz, 1H), 4.17–4.01 (m, 3H), 3.99–3.81 (m, 4H), 3.52 (td, *J* = 7.2, 2.2 Hz, 2H), 3.39 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.31 (dd, *J* = 9.8, 7.1 Hz, 1H), 2.99–2.88 (m, 1H), 2.53–2.43 (m, 1H), 2.21–2.11 (m, 1H), 1.78–1.68 (m, 1H), 1.64–1.53 (m, 2H), 1.38–1.17 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 179.6, 179.4, 166.2, 152.5, 134.9, 126.2, 124.7, 121.2, 121.1, 74.6, 74.5, 62.5, 61.7, 50.2, 42.6, 39.4, 39.3, 37.9, 36.9, 31.8, 29.2, 27.09, 27.06, 22.6, 14.1. IR (thin film, cm⁻¹): 3392, 2926, 2855, 1681, 1426, 1353, 999, 756, 728. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₅H₃₄N₂O₅S₂Na, 529.1801; found, 529.1798. HPLC (45:55 hexane/ⁱPrOH, Daicel CHIRALPAK IA): 91:9 er, *t*_R (minor) 4.4 min, *t*_R (major) 6.6 min. [α]_D = -65.2 (c 0.007, CHCl₃). TLC (20:1 DCM/MeOH): *R*_f = 0.5.

Procedure for the Preparation of 7. To a CHCl₃ (0.7 mL) solution of **4b** (50.0 mg, 0.16 mmol), the catalyst (3.9 mg, 0.02 mmol), and Na₂SO₄ (78.3 mg, 0.55 mmol) was added propionic anhydride (22 μL, 0.17 mmol) at room temperature. The reaction was allowed to stir for 5 days and stopped by removal of the solvent under reduced pressure. Purification via column chromatography using a gradient from 1:1 to 1:2 hexanes/ethyl acetate afforded **7** as a clear oil (26.0 mg, 0.07 mmol, 44% yield, 14:1 dr, 80:20 er). The absolute configuration is unassigned. Note that some epimerization was observed after column chromatography, resulting in the 14:1 dr. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.39–7.35 (m, 2H), 7.33–7.29 (m, 2H), 7.29–7.25 (m, 1H), 4.81 (dd, *J* = 11.4, 6.2 Hz, 1H), 4.65 (s, 2H), 4.58 (dd, *J* = 11.4, 8.8 Hz, 1H), 4.05–3.99 (m, 1H), 3.96–3.89 (m, 1H), 3.48–3.41 (m, 1H), 3.28 (d, *J* = 4.8 Hz, 1H), 3.14–3.08 (m, 2H), 3.00 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.67–2.60 (m, 2H), 2.35 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 178.9, 177.1, 174.1, 135.3, 128.5, 128.4, 127.8, 63.7, 62.8, 52.4, 51.9, 42.5, 38.9, 38.3,

37.0, 35.1, 27.5, 9.0. IR (thin film, cm⁻¹): 3444, 2943, 1694, 1353, 1187, 1082, 1018, 881. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₀H₂₃NO₆Na, 396.1418; found, 396.1418. HPLC (65:35 hexane/ⁱPrOH, Daicel CHIRALPAK IC): 82:18 er, *t*_R (major) 16.5 min, *t*_R (minor) 29.6 min. [α]_D = -5.08 (c 0.01, CHCl₃). TLC (1:2 hexanes/ethyl acetate): *R*_f = 0.1.

Procedure for the Preparation of 8. Acetic anhydride (34 μL, 0.36 mmol) was added to a dichloromethane (0.8 mL) solution of **5b** (52.0 mg, 0.16 mmol) and DMAP (2.0 mg, 0.02 mmol) at room temperature, and the reaction was allowed to stir overnight. The solvent was subsequently removed under reduced pressure, and the crude material was purified using column chromatography (1:1 hexanes/ethyl acetate) to obtain **8** as a clear oil (50.0 mg, 0.13 mmol, 76% yield). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.35–7.26 (m, 5H), 4.70 (ddd, *J* = 11.1, 3.9, 1.2 Hz, 2H), 4.62 (s, 2H), 4.37 (ddd, *J* = 11.1, 6.8, 1.1 Hz, 2H), 3.28 (s, 2H), 2.84–2.77 (m, 2H), 2.40–2.33 (m, 2H), 2.10 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 177.8, 170.7, 135.4, 128.7, 128.1, 64.6, 51.2, 42.4, 36.8, 34.7, 20.8. IR (thin film, cm⁻¹): 3648, 3456, 2951, 2359, 1698, 1401, 1235, 1040. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₁H₂₃NO₇Na, 424.1367; found, 424.1349. TLC (1:1 hexanes/ethyl acetate): *R*_f = 0.4.

Procedure for the Preparation of 9. A mixture of **8** (50 mg, 0.13 mmol), porcine pancreatic lipase (100 mg), acetone (2.5 mL), and pH 6.5 phosphate buffer (5 mL) was stirred for 5 days at room temperature. Ethyl acetate (5 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organics were combined, dried with sodium sulfate, and concentrated under reduced pressure. Purification via column chromatography using hexanes/ethyl acetate 1:1 to 1:2 afforded **9** as a clear oil (31.0 mg, 0.09 mmol, 69% yield, 88:12 er). The absolute configuration is unassigned. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.36–7.24 (m, 5H), 4.72 (ddd, *J* = 11.1, 3.9, 1.9 Hz, 1H), 4.63 (d, *J* = 1.9 Hz, 2H), 4.42–4.34 (m, 1H), 4.11–4.03 (m, 1H), 4.03–3.94 (m, 1H), 3.29 (q, *J* = 4.6 Hz, 2H), 2.92–2.77 (m, 3H), 2.40–2.33 (m, 1H), 2.28–2.21 (m, 1H), 2.10 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 179.4, 178.0, 170.8, 135.3, 128.8, 128.1, 65.2, 64.6, 51.7, 51.2, 42.5, 38.4, 37.1, 36.9, 36.6, 34.8, 20.8. IR (thin film, cm⁻¹): 3502, 2926, 1697, 1400, 1241, 1176, 1037. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₉H₂₁NO₆Na, 382.1261; found, 382.1251. HPLC (65:35 hexane/ⁱPrOH, Daicel CHIRALPAK IC): 88:12 er, *t*_R (major) 23.1 min, *t*_R (minor) 34.6 min. [α]_D = +20.9 (c 0.01, CHCl₃). TLC (1:1 hexanes/ethyl acetate): *R*_f = 0.2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00523.

Crystallographic data for **5d** (CIF)

Mechanistic experiments and spectral data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jsj@unc.edu.

ORCID

Jeffrey S. Johnson: 0000-0001-8882-9881

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the National Science Foundation (CHE-1402917 and CHE-1665008) for financial support. D.M.M. acknowledges an NSF Graduate Research Fellowship. X-ray crystallography was performed by Dr. Peter White (UNC).

REFERENCES

- (1) (a) Marco-Contelles, J.; Molina, M. T.; Anjum, S. Naturally Occurring Cyclohexane Epoxides: Sources, Biological Activities, and Synthesis. *Chem. Rev.* 2004, 104, 2857. (b) Chida, N.; Sato, T. Synthesis of Natural Products Containing Cyclohexane Units Utilizing the Ferrier Carbocyclization Reaction. *Chem. Rev.* 2014, 14, 592. (c) Yang, X.; Wang, J.; Li, P. Recent progress on asymmetric organocatalytic construction of chiral cyclohexenone skeletons. *Org. Biomol. Chem.* 2014, 12, 2499.
- (2) (a) Kaliappan, K.; Subba Rao, G. S. R. Synthesis based on cyclohexadienes. Part 23. Total synthesis of 5-*epi*-pupukean-2-one. *J. Chem. Soc., Perkin Trans. 1* 1997, 3387. (b) Roche, S. P.; Porco, J. A., Jr. Dearomatization Strategies in the Synthesis of Complex Natural Products. *Angew. Chem., Int. Ed.* 2011, 50, 4068.
- (3) (a) Reisman, S. E.; Nani, R. R.; Levin, S. Buchner and Beyond: Arene Cyclopropanation as Applied to Natural Product Total Synthesis. *Synlett* 2011, 2011, 2437. (b) Mackay, W. D.; Johnson, J. S. Kinetic Separation and Asymmetric Reactions of Norcaradiene Cycloadducts: Facilitated Access via H₂O-Accelerated Cycloaddition. *Org. Lett.* 2016, 18, 536.
- (4) Hudlicky, T.; Reed, J. W. On the Merits of Biocatalysis and the Impact of Arene *cis*-Dihydrodiols on Enantioselective Synthesis. *Synlett* 2009, 2009, 685.
- (5) (a) Jerina, D. M.; Daly, J. W.; Witkop, B.; Zaltzman-Nirenberg, P.; Udenfriend, S. The role of arene oxide-oxepin systems in the metabolism of aromatic substrates. III. Formation of 1,2-naphthalene oxide from naphthalene by liver microsomes. *J. Am. Chem. Soc.* 1968, 90, 6525. (b) Jerina, D. M.; Daly, J. W. Arene Oxides: A New Aspect of Drug Metabolism. *Science* 1974, 185, 573. (c) Bruice, T. C.; Bruice, P. Y. Solution chemistry of arene oxides. *Acc. Chem. Res.* 1976, 9, 378.
- (6) de Visser, S. P.; Shaik, S. A Proton-Shuttle Mechanism Mediated by the Porphyrin in Benzene Hydroxylation by Cytochrome P450 Enzymes. *J. Am. Chem. Soc.* 2003, 125, 7413.
- (7) (a) Hayes, D. M.; Nelson, S. D.; Garland, W. A.; Kollman, P. A. A molecular orbital study of the benzene oxide-oxepin valence isomerization. *J. Am. Chem. Soc.* 1980, 102, 1255. (b) Bock, C. W.; George, P.; Stezowski, J. J.; Glusker, J. P. Calculating atomic fast-electron scattering amplitudes by means of electron wave functions. *Struct. Chem.* 1990, 1, 33. (c) Brandt, P.; Jia, Z. S.; Thibblin, A. Kinetic and Thermodynamic Stability of Naphthalene Oxide and Related Compounds. A Comparative Microcalorimetric and Computational (DFT) Study. *J. Org. Chem.* 2002, 67, 7676. (d) Kassaei, M. Z.; Arshadi, S.; Ahmadi-Taheri, N. Substituent effects on tautomerization of oxepine to benzene oxide: a Hammett study via ab initio. *J. Mol. Struct.: THEOCHEM* 2005, 715, 107.
- (8) Jeffrey, A. M.; Yeh, H. J. C.; Jerina, D. M.; De Marinis, R. M.; Foster, C. H.; Piccolo, D. E.; Berchtold, G. A. Stereochemical course in reactions between nucleophiles and arene oxides. *J. Am. Chem. Soc.* 1974, 96, 6929. (b) Bertozzi, F.; Crotti, P.; Del Moro, F.; Feringa, B. L.; Macchia, F.; Pineschi, M. Unprecedented catalytic enantioselective trapping of arene oxides with dialkylzinc reagents. *Chem. Commun.* 2001, 2606.
- (9) Foster, C. H.; Berchtold, G. A. Synthesis of trans-benzene trioxide. *J. Am. Chem. Soc.* 1972, 94, 7939.
- (10) (a) Rastetter, W. H. sym-Oxepin oxide. *J. Am. Chem. Soc.* 1976, 98, 6350. (b) Gillard, J. R.; Newlands, M. J.; Bridson, J. N.; Burnell, D. J. π -Facial stereoselectivity in the Diels-Alder reactions of benzene oxides. *Can. J. Chem.* 1991, 69, 1337. (c) Cossu, S.; Battaglia, S.; De Lucchi, O. Barrelene, a New Convenient Synthesis. *J. Org. Chem.* 1997, 62, 4162. (d) Henderson, A. P.; Mutlu, E.; Leclercq, A.; Bleasdale, C.; Clegg, W.; Henderson, R. A.; Golding, B. T. Trapping of benzene oxide-oxepin and methyl-substituted derivatives with 4-phenyl- and 4-pentafluorophenyl-1,2,4-triazoline-3,5-dione. *Chem. Commun.* 2002, 1956.
- (11) Vogel, E.; Günther, H. Benzene Oxide-Oxepin Valence Tautomerism. *Angew. Chem., Int. Ed. Engl.* 1967, 6, 385.
- (12) For general reviews on desymmetrization chemistry to access complex molecules, see: (a) García-Urdiales, E.; Alfonso, I.; Gotor, V. Enantioselective Enzymatic Desymmetrizations in Organic Synthesis. *Chem. Rev.* 2005, 105, 313. (b) Díaz de Villegas, M. D.; Gálvez, J. A.; Etayo, P.; Badorrey, R.; López-Ram-de-Viú, P. Recent advances in enantioselective organocatalyzed anhydride desymmetrization and its application to the synthesis of valuable enantiopure compounds. *Chem. Soc. Rev.* 2011, 40, 5564. (c) Wang, M.; Feng, M.; Tang, B.; Jiang, X. Recent advances of desymmetrization protocol applied in natural product total synthesis. *Tetrahedron Lett.* 2014, 55, 7147. (d) Borisssov, A.; Davies, T. Q.; Ellis, S. R.; Fleming, T. A.; Richardson, M. S.; Dixon, D. J. Organocatalytic enantioselective desymmetrisation. *Chem. Soc. Rev.* 2016, 45, 5474. (e) Merad, J.; Candy, M.; Pons, J.; Bressy, C. Catalytic Enantioselective Desymmetrization of Meso Compounds in Total Synthesis of Natural Products: Towards an Economy of Chiral Reagents. *Synthesis* 2017, 49, 1938.
- (13) (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. Enantioselective desymmetrisation of achiral epoxides. *Tetrahedron* 1996, 52, 14361. (b) Wang, P.-A. Organocatalyzed enantioselective desymmetrization of aziridines and epoxides. *Beilstein J. Org. Chem.* 2013, 9, 1677.
- (14) (a) Díaz de Villegas, M. D.; Gálvez, J. A.; Badorrey, R.; López-Ram-de-Viú, P. Organocatalyzed Enantioselective Desymmetrization of Diols in the Preparation of Chiral Building Blocks. *Chem. - Eur. J.* 2012, 18, 13920. (b) Enríquez-García, A.; Kündig, E. P. Desymmetrisation of meso diols mediated by non-enzymatic acyl transfer catalysts. *Chem. Soc. Rev.* 2012, 41, 7803.
- (15) (a) Studer, A.; Schleich, F. Desymmetrization and Diastereotopic Group Selection in 1,4-Cyclohexadienes. *Synlett* 2005, 3033. (b) Zeng, X.; Cao, Z.; Wang, Y.; Zhou, F.; Zhou, J. Catalytic Enantioselective Desymmetrization Reactions to All-Carbon Quaternary Stereocenters. *Chem. Rev.* 2016, 116, 7330.
- (16) (a) Boyd, D. R.; Hamilton, J. T. G.; Sharma, N. D.; Harrison, J. S.; McRoberts, W. C.; Harper, D. B. Isolation of a stable benzene oxide from a fungal biotransformation and evidence for an 'NIH shift' of the carbomethoxy group during hydroxylation of methyl benzoates. *Chem. Commun.* 2000, 1481. (b) Boyd, D. R.; Sharma, N. D.; Ljubez, V.; McGeehin, P. K. M.; Stevenson, P. J.; Blain, M.; Allen, C. C. R. Chemoenzymatic synthesis of monocyclic areneoxides and arene hydrates from substituted benzene substrates. *Org. Biomol. Chem.* 2013, 11, 3020.
- (17) (a) Berndt, T.; Böge, O.; Herrmann, H. On the formation of benzene oxide/oxepin in the gas-phase reaction of OH radicals with benzene. *Chem. Phys. Lett.* 1999, 314, 435. (b) Broyles, D. A.; Carpenter, B. K. Experimental Detection of One Case of Benzene Epoxidation by a Peroxy Radical and Computational Prediction of Another. *J. Org. Chem.* 2005, 70, 8642.
- (18) CCDC 1813010 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Center via www.cam.ac.uk/data_request/cif.
- (19) (a) Craig, D. The Diels-Alder Reactions of the Piperylene Isomers with Maleic Anhydride and Fumaric Acid. *J. Am. Chem. Soc.* 1950, 72, 1678. (b) Brettell, R.; Cummings, D. P. A synthetic approach to the indole alkaloid apparicine. Synthesis of the ring skeleton. *J. Chem. Soc., Perkin Trans. 1* 1977, 2385.
- (20) Wang, Z.; Law, W. K.; Sun, J. Chiral Phosphoric Acid Catalyzed Enantioselective Desymmetrization. *Org. Lett.* 2013, 15, 5964.
- (21) Birman, V. B.; Li, X. Benzotetramisole: A Remarkably Enantioselective Acyl Transfer Catalyst. *Org. Lett.* 2006, 8, 1351.
- (22) Schoffers, E.; Golebiowski, A.; Johnson, C. R. Enantioselective synthesis through enzymatic asymmetrization. *Tetrahedron* 1996, 52, 3769.
- (23) The absolute configurations for the chiral compounds in Scheme 4 are unassigned.
- (24) Yamashita, S.; Mase, N.; Takabe, K. Chemoenzymatic total synthesis and determination of the absolute configuration of (S)-nebracetam. *Tetrahedron: Asymmetry* 2008, 19, 2115.
- (25) Wang, Z.; Kim, C.; Facchetti, A.; Marks, T. J. Anthracenedi-carboximides as Air-Stable N-Channel Semiconductors for Thin-Film Transistors with Remarkable Current On-Off Ratios. *J. Am. Chem. Soc.* 2007, 129, 13362.

- (26) Garad, D. N.; Tanpure, S. D.; Mhaske, S. B. Radical-mediated dehydrative preparation of cyclic imides using $(\text{NH}_4)_2\text{S}_2\text{O}_8$ –DMSO: application to the synthesis of vernakalant. *Beilstein J. Org. Chem.* 2015, 11, 1008.
- (27) Molina, C. L.; Chow, C. P.; Shea, K. J. Type 2 Intramolecular *N*-Acylazo Diels–Alder Reaction: Regio- and Stereoselective Synthesis of Bridgehead Bicyclic 1,2-Diazines. *J. Org. Chem.* 2007, 72, 6816.
- (28) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. Enantioselective Organocatalytic Reductive Amination. *J. Am. Chem. Soc.* 2006, 128, 84.