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

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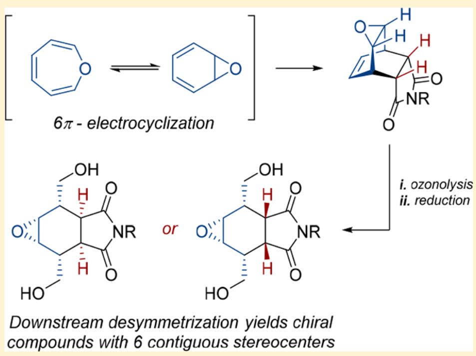
Supporting Information

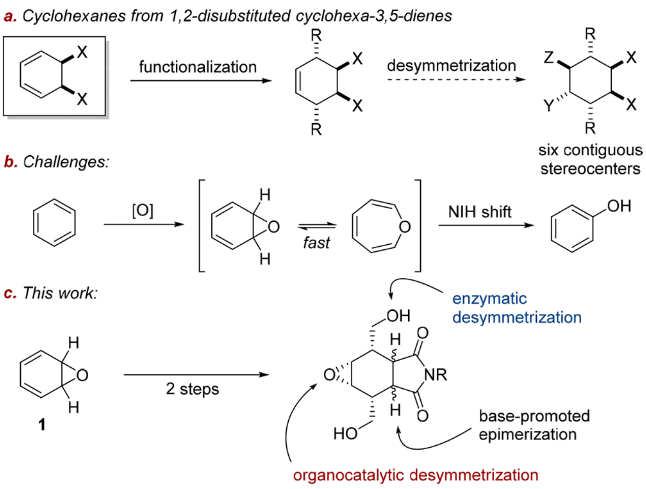
ABSTRACT: Ozonolysis of the Diels−Alder adducts derived from benzene oxides and *N*-alkylmaleimides resulted in fully substituted, *meso* bicyclic systems bearing six contiguous stereocenters, isolated as diols upon reductive workup with $NaBH_4$. Variation in the workup allowed for isolation of two 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 opening[8] (including one enantioselective case),[8b] diene functionalization,[9] and Diels−Alder reactivity[10] 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]

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



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 formation[15] 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

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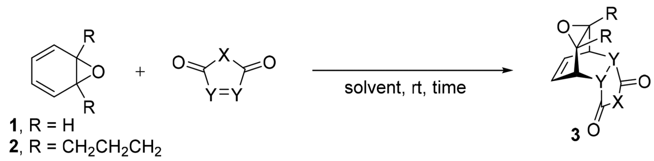
Table 1. Synthesis of *meso* Bicyclic Compounds from Benzene Oxides 1 and 2



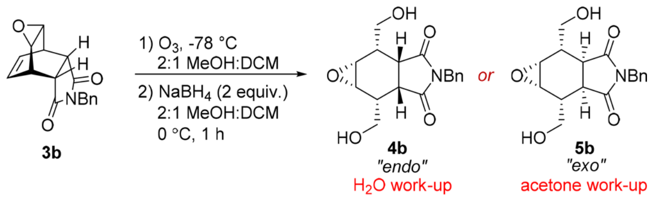
entry	product	R	X	Y	solvent	time (h)	yield (%)
1	**3a**	H	O	CH	Et_2O	72	71
2	**3b**	H	NBn	CH	Et_2O	24	50
3	**3c**	H	NPh	CH	Et_2O	24	53
4	**3d**	H	NC_8H_{17}	CH	Et_2O	72	61
5	**3e**	H	NPh	N	acetone	1	65
6	**3f**	$CH_2CH_2CH_2$	NBn	CH	Et_2O	24	57

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 $NaBH_4$ workup (Scheme 2). Using Me_2S for the workup conditions rendered a labile putative dialdehyde that decomposed readily. Unexpectedly, the conditions by which the $NaBH_4$ was quenched had an effect in the stereoselectivity of the reaction. Addition of water to quench the remaining $NaBH_4$ 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]

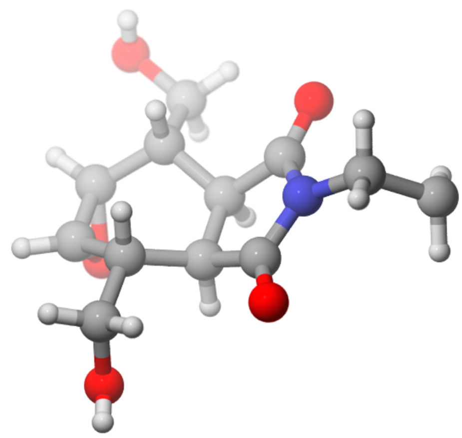


Figure 1. X-ray structure of succinimide **5d**. The *n*-octyl chain was truncated for better visualization.

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).

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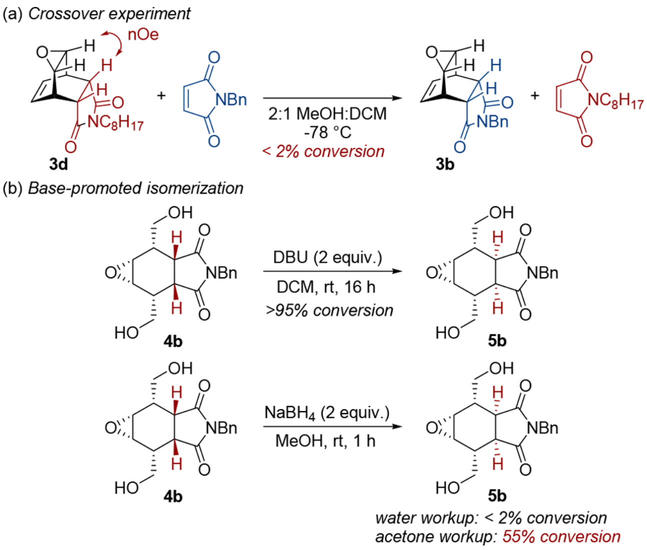
Scheme 3. Experiments Probing the Mechanism of Diastereomerization



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-mercaptothiazole resulted in the opening of the epoxide **4d**, providing alcohol **6** in 63% yield and 90:10 er

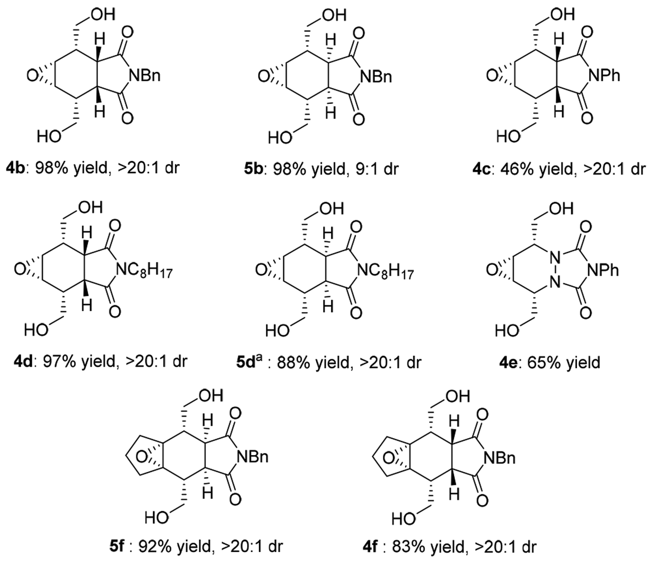
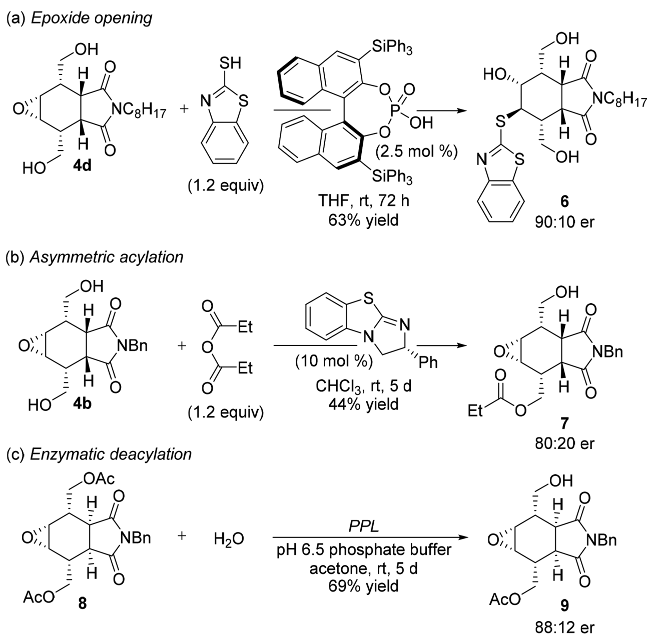


Figure 2. Scope of the ozonolysis reaction of *meso* bicyclic compounds. Footnote a represents the compound after DBU stir.

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

Scheme 4. Enantioselective Desymmetrization of *meso* Products



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

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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 (^{1}H NMR, ^{13}C NMR, ^{19}F NMR) were recorded at the following frequencies: ^{1}H NMR at 400 or 600 MHz, ^{13}C NMR at 101 or 151 MHz with solvent resonance as the internal standard (^{1}H NMR $CDCl_3$ at 7.26 ppm and ^{13}C NMR $CDCl_3$ at 77.0 ppm). ^{1}H 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 catalyst[21] 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 $Na_2S_2O_5$ (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 × 100 mL) and brine (100 mL × 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] ^{1}H 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-1*H*-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-1*H*-3a,7a-epoxyindene[9] (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] ^{1}H 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 × 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 R = $CH_2CH_2CH_2$.

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] ^{1}H 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: ^{1}H 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*: $[M + Na]^+$ calcd for $C_{17}H_{15}NO_3Na$, 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] ^{1}H 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: ^{1}H 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-

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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] ^{1}H 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-1*H*-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: ^{1}H 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 × 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 × 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: ^{1}H 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 $C_{17}H_{20}NO_5$, 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: ^{1}H 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 $C_{17}H_{20}NO_5$, 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: ^{1}H 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, 62.7, 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 $C_{16}H_{17}NO_5Na$, 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: ^{1}H 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 $C_{18}H_{29}NO_5Na$, 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 μL, 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 × 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: ^{1}H 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 $C_{18}H_{30}NO_5$, 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: ^{1}H 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 $C_{14}H_{15}N_3O_5Na$, 328.0904; found, 328.0893. Mp: 119−122 °C. TLC (20:1 DCM/MeOH): R_f = 0.2.

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(3R,4R,4S,7R,8S,8S)-2-Benzyl-4,8-bis(hydroxymethyl)hexahydro-1H,5H-4a,7a-epoxycyclopenta[f]isoindole-1,3(2H)-dione ***(4f)***. The title compound was prepared according to general procedure B using **3f** (50 mg, 0.16 mmol), $NaBH_4$ (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: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$): 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 $C_{20}H_{23}NO_5Na$, 380.1468; found, 380.1467. TLC (20:1 DCM/MeOH): R_f = 0.3.

(3aR,4S,4aR,7aS,8R,8aS)-2-Benzyl-4,8-bis(hydroxymethyl)-hexahydro-1H,5H-4a,7a-epoxycyclopenta[f]isoindole-1,3(2H)-dione ***(5f)***. The title compound was prepared according to general procedure C using **3f** (50 mg, 0.16 mmol), $NaBH_4$ (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: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{20}H_{23}NO_5Na$, 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: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{25}H_{34}N_2O_5S_2Na$, 529.1801; found, 529.1798. HPLC (45:55 hexane/^{i}PrOH, Daicel CHIRALPAK IA): 91:9 er, t_R (minor) 4.4 min, t_R (major) 6.6 min. $[\alpha]_D$ = −65.2 (c 0.007, $CHCl_3$). TLC (20:1 DCM/MeOH): R_f = 0.5.

Procedure for the Preparation of ***7***. To a $CHCl_3$ (0.7 mL) solution of **4b** (50.0 mg, 0.16 mmol), the catalyst (3.9 mg, 0.02 mmol), and Na_2SO_4 (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: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{20}H_{23}NO_6Na$, 396.1418; found, 396.1418. HPLC (65:35 hexane/^{i}PrOH, Daicel CHIRALPAK IC): 82:18 er, t_R (major) 16.5 min, t_R (minor) 29.6 min. $[\alpha]_D$ = −5.08 (c 0.01, $CHCl_3$). 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: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{21}H_{23}NO_7Na$, 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: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{19}H_{21}NO_6Na$, 382.1261; found, 382.1251. HPLC (65:35 hexane/^{i}PrOH, Daicel CHIRALPAK IC): 88:12 er, t_R (major) 23.1 min, t_R (minor) 34.6 min. $[\alpha]_D$ = +20.9 (c 0.01, $CHCl_3$). 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)

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Notes

The authors declare no competing financial interest.

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