Journal of
Medicinal Chemistry

Article

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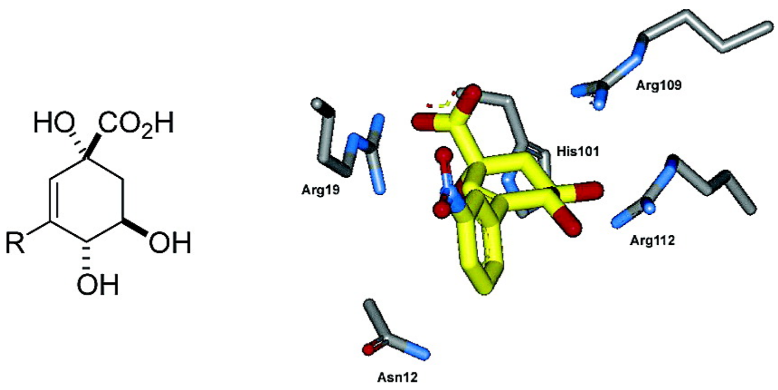
J. Med. Chem., **2005**, 48 (15), 4871-4881• DOI: 10.1021/jm0501836 • Publication Date (Web): 25 June 2005



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Structure-Based Design, Synthesis, and Biological Evaluation of Inhibitors of *Mycobacterium tuberculosis* Type II Dehydroquinase

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Received February 25, 2005

The syntheses by Suzuki cross-coupling of 12 5-aryl analogues of the known inhibitor (1*R*,3*R*,4*R*)-1,3,4-trihydroxycyclohex-5-en-1-carboxylic acid are reported. These compounds were found to be reversible competitive inhibitors against *Mycobacterium tuberculosis* type II dehydroquinase, the third enzyme of the shikimic acid pathway. The most potent inhibitor, the 3-nitrophenyl derivative, has a K_i of 54 nM, over 180 times more potent than the reported inhibitor (1*R*,3*R*,4*R*)-5-fluoro-1,3,4-trihydroxycyclohex-5-en-1-carboxylic acid and more than 700 times lower than the K_M of the substrate, making it the most potent known inhibitor against any type II dehydroquinase. Docking studies using GOLD (version 2.2) indicated a key electrostatic binding interaction between the aromatic rings and Arg19, a residue that has been identified as essential for enzyme activity.

Introduction

Although effective chemotherapeutic agents have been developed, *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), continues to be the greatest single infectious cause of mortality worldwide, killing roughly two million people annually (one person dies every 10 s).[1] The World Health Organization (WHO) has estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis*.[2] Each untreated person with active TB disease will infect on average of 10−15 people every year, but people infected with TB bacilli will not necessarily become sick with the disease. The TB bacilli may remain in the body for decades without causing the symptoms of tuberculosis.[3] TB is a leading cause of death among people who are HIV-positive (13% of AIDS deaths worldwide).[4] The synergy between tuberculosis and the AIDS epidemic and the surge of multidrug-resistant isolates of *M. tuberculosis* have reaffirmed tuberculosis as a primary public health threat. It has been predicted that by 2020 one billion people will be newly infected if new anti-TB treatments are not developed. It is therefore necessary to discover new, safe, and more efficient antibiotics against this disease.

The shikimate pathway is the biosynthetic route to the aromatic amino acids L-phenylalanine, L-tryptophan, and L-tyrosine, as well as precursors to the folate coenzymes, alkaloids, and vitamins, and many other aromatic compounds.[5] This pathway is present in bacteria, fungi, and plants and has been recently discovered in apicomplexan parasites *Plasmodium falciparum* (malaria), *Toxoplasma gondii*, and *Cryptosporidium parvum*.[6] The absence of the pathway in mammals, combined with its essential nature in certain microorganisms, makes the shikimic acid pathway enzymes attractive targets for the development of new antibiotics and herbicides. In fact, glyphosate [*N*-(phosphomethyl)glycine], the active ingredient in the well-known herbicides RoundUp and Tumbleweed and a specific inhibitor of the sixth enzyme of the shikimate pathway (EPSP synthase),[7] was shown to be active in vitro against malaria.[6a] Also, (6*R*)- and (6*S*)-6-fluoroshikimic acids have shown antimicrobial activity against *Escherichia coli*, the latter being the most potent one.[8] Here, we report a series of compounds active against *Mycobacterium tuberculosis* type II dehydroquinase, the third enzyme of the shikimic acid pathway.

The enzyme dehydroquinase (3-dehydroquinate dehydratase, EC 4.2.1.10) catalyzes the reversible dehydration of 3-dehydroquinic acid (**1**) to form 3-dehydroshikimic acid (**2**) (Scheme 1). This reaction is part of two metabolic pathways: the biosynthetic shikimate pathway and the catabolic quinate pathway.[9] There are two distinct types of enzymes, known as type I and type II, which have different biochemical and biophysical properties and show no sequence similarity. The type I enzyme (typically *Salmonella typhi* and *Escherichia coli*)[10] found in plants, fungi, and many bacterial species is exclusively biosynthetic, whereas the type II enzyme (*Streptomyces coelicolor*, *Mycobacterium tuberculosis*, *Aspergillius nidulans*, *Helicobacter pylori*, *Neurospora crassa*)[11] has both biosynthetic and catabolic roles. More importantly, these enzymes utilize completely different mechanisms to catalyze the same overall reaction. The type I enzyme mechanism involves covalent imine intermediates between the enzyme (Lys170 in *E. coli*) and the substrate and proceeds with syn stereochemistry.[12] In contrast, type II reaction proceeds through an enol intermediate with overall anti stereochemistry

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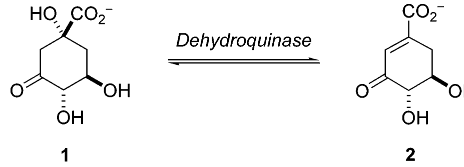
10.1021/jm0501836 CCC: $30.25

Scheme 1. Conversion of 3-Dehydroquinic Acid (**1**) to 3-Dehydroshikimic Acid (**2**) Catalyzed by Dehydroquinase



(Scheme 2).[13] Two residues, Arg19 and Tyr24, have been identified by chemical modification and site-directed mutagenesis studies as being essential for enzyme activity.[14] Both residues are on the flexible loop that closes over the active site upon substrate binding. It has been suggested that Arg19 is involved in stabilization of the enol intermediate. A conserved molecule of water close to the carbonyl group stabilizes the enol intermediate, and it is held in a specific orientation by hydrogen bonds to Asn12, the carbonyl group of Pro11, and the main chain amide of Gly77. The final step is the acid-catalyzed elimination of the C1 hydroxyl group catalyzed by His101. These mechanistic and stereochemical distinctions have allowed the design and the synthesis of compounds that are specific to either type I[15] or type II[16] enzymes.

Because the elimination mechanism of the type II enzymes proceeds via an enol intermediate characterized by ring-flattening due to the π-system formed between C2 and C3 and by the increased H-bonding of the enol oxygen formed, compounds that mimicked the enol intermediate were likely to show inhibitory properties. Both of these features have been exploited for the design of the first generation of inhibitors. Abell *et al.* reported that analogues **3a**, **3b**, and **3c** are competitive reversible inhibitors of *M. tuberculosis* type II dehydroquinase with a K_i of 200 μM, 10 μM, and 20 μM, respectively (Figure 1).[16a,c,17] The crystal structures of *M. tuberculosis* dehydroquinase apoenzyme[18] and the enzyme in complex with inhibitors **3a**[19] and **3c**[20] have been recently solved. The important observation that compounds with a double bond between C5 and C6 bind in a manner predicted for transition-state mimics encouraged us to design the next generation of inhibitors.

We have reported previously that the incorporation of substituted benzyl moieties in C1 or C4 hydroxyl groups of the inhibitor **3a** results in the competitive inhibition of *Streptomyces coelicolor* type II dehydroquinase.[16d] The key binding interactions for the benzyl groups appear to be π-stacking against Tyr28 and possibly electrostatic interactions with Arg23. Tyr28 performs the proton abstraction, and its pK_a is mediated by the proximity of the side chain of Arg113 and possibly of Arg23. We therefore decided to explore the idea of making more potent inhibitors against *M. tuberculosis* type II dehydroquinase by incorporating substituted aryl groups in the C5 of inhibitor **3a**. Herein, we describe the synthesis of 12 new analogues **4a**–**l** (Figure 1) using palladium-catalyzed cross-coupling reactions. The results of inhibition studies of these compounds against *M. tuberculosis* type II dehydroquinase and the molecular docking studies using GOLD (version 2.2) are also described.

Results and Discussion

Synthesis of Compounds 4a–l. The strategy used involved the introduction of the aromatic ring in **4a**–**l** by Suzuki cross-coupling reactions between diverse substituted phenyl- and arylboronic acids and vinyl triflate **6**, which was synthesized from a cheap and commercially available (−)-quinic acid (**5**)[21] as a chiral template (Scheme 3).

The synthesis of the key intermediate, the vinyl triflate **6**, was achieved in four steps from previously reported benzyl lactone **7**,[22] as outlined in Scheme 4. First, treatment of diol **7** with TBSOTf in pyridine afforded silyl ether **8** in 97% yield. Deprotection of the equatorial secondary hydroxyl group in **8** was achieved by catallytic hydrogenolysis. Although the reaction can be carried out using palladium-on-carbon, the best results were obtained using palladium hydroxide in methanol. The free hydroxyl group in **9** was readily oxidized using PDC in the presence of 4 Å activated molecular sieves to afford ketone **10** in 95% yield. Finally, the key intermediate **6** was synthesied by enolization of the ketone **10** and reaction with triflimide. Different bases (LDA, KHMDS, LHMDS), temperatures, and solvents (THF, DMF, DMF/toluene) were employed. Using KHMDS in a mixture of DMF/toluene (1:1.1) gave the desired vinyl triflate **6** in 80% yield.

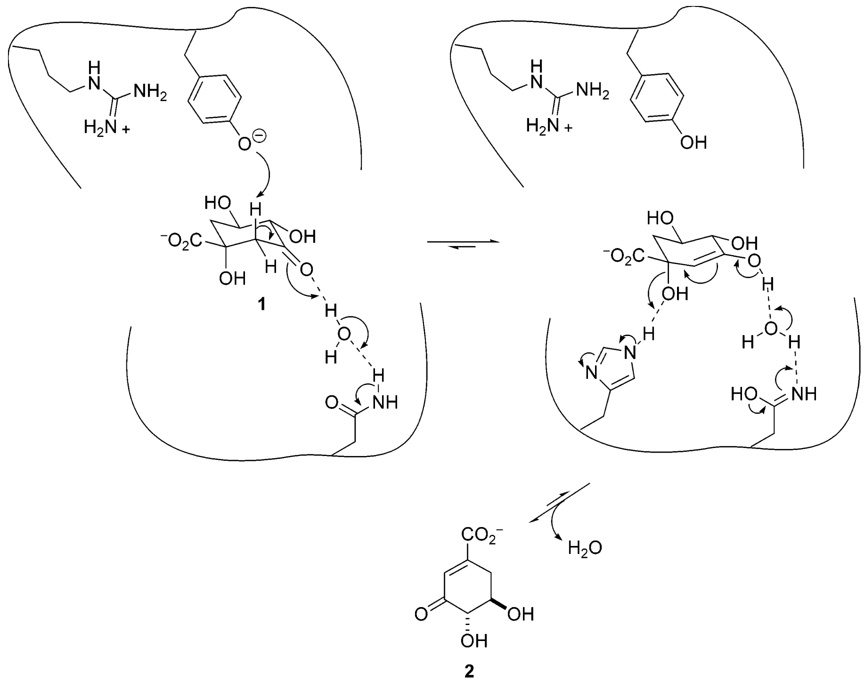
The key step of the synthesis was the carbon–carbon bond formation between the vinyl triflate **6** and diverse boronic acids. The reaction was performed in THF in the presence of Et_3N (3 equiv) and $(dba)_3Pd_2 \cdot CHCl_3$ catalyst (7.5%).[23] The corresponding vinylaryl derivatives **11** were obtained in good yields of 61–96% after column chromatography (Scheme 5, Table 1). Attempts to synthesize **11k** using the above conditions afforded mainly starting material. However, by use of a 3-pyridine boronic acid ester, $Pd(PPh_3)_4$ as catalyst in the presence of K_3PO_4 afforded the desired pyridine **11k** in good yield (Table 1, entry 11).

Finally, conversion of the cross-coupling products **11** to the desired acids **4** was achieved by a two-step reaction sequence. The first step is deprotection of the TBS groups with TBAF (60–97%), and the second step is basic hydrolysis of the corresponding lactone, followed by treatment with Amberlite IR-120 (H^+) ion-exchange resin (83–99%).

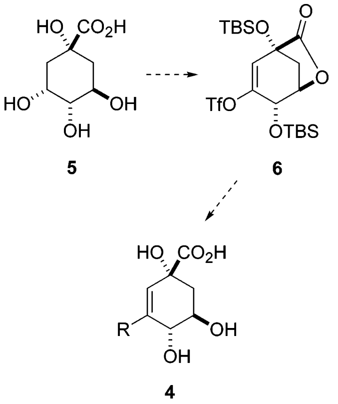
Assay Results. The 12 acids **4a**–**l** were assayed in the presence of 3-dehydroquinic acid (**1**) for their inhibitory properties against *M. tuberculosis* type II dehydroquinase. The inhibition data are summarized in Table 2. The UV spectrophotometric assay was used to measure the initial rate of product formation, detecting the enone–carboxylate chromophore at 234 nm in 3-dehydroshikimic acid (**2**). The K_i values were obtained from Dixon plots ($1/v$ vs [I]).

All the compounds were shown to be reversible competitive inhibitors of *M. tuberculosis* type II dehydroquinase. All the analogues, except three of them, 4-CF_3 **4c**, 3-OH **4f**, and 3-CO_2H **4h**, were found to be more potent than the original inhibitors **3a** (200 μM), **3b** (10 μM), and **3c** (20 μM). The 3-nitro derivative **4g** was the most potent compound with a low K_i of 54 nM compared to the reported inhibitors **3a**, **3b**, and **3c** and considerably below the K_M of the substrate (40 μM). The thiophene derivative **4j** also had a high affinity of 590

Scheme 2. Proposed E1CB Mechanism for the Enzymatic Conversion of 3-Dehydroquinic Acid (**1**) to 3-Dehydroshikimic Acid (**2**) Catalyzed by Type II Dehydroquinase Indicating the Residues Involved in the Catalysis



Scheme 3



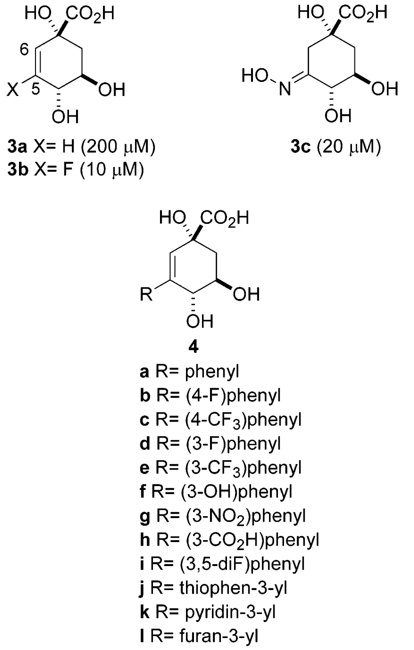
nM. No significant differences in activity were found between fluorophenyl analogues, the 3-substituted being slightly more potent than the 4-substituted. The 3-carboxy derivative **4h** was a surprisingly poor inhibitor with a K_i of 150 μM.

Docking Studies. Ligands **4a**−**l** were docked in the active site of *M. tuberculosis* type II dehydroquinase using the program GOLD (version 2.2).[24]

The apoenzyme structure indicates that the catalytically important domain is disordered with no interpretable electron density visible between residues 19 and 26, where Arg19 and Tyr24 are located. Both residues have been previously identified by chemical modification and site-directed mutagenesis studies as being essential for enzyme activity.[25] Arg19 is not observed as well in the crystal structure of the enzyme complexed with the inhibitor **3a**.[19] However, in the crystal structures of the enzyme complexed with sulfate[26] and with the oxime inhibitor **3c**,[20] this arginine is visible and is positioned in the active site of the enzyme. Therefore, the latter crystal structure was used for this study.

The molecule of inhibitor **3c** and all the water molecules were removed from the structure. No energy minimization was performed on the enzyme. The structures of the inhibitors were prepared using Gaussian 98W[27] and energy-minimized using AM1. All the inhibitors were docked as their carboxylate anions, and 25 independent GOLD runs were performed for each ligand. The GoldScore scoring function was used.

Ligands **3a** and **3c** were docked as a control, and the results were compared to the enzyme−inhibitor complex. Both ligands docked similarly at the same site, and their positions in the active site coincided with the position of the oxime inhibitor **3c** in the crystal structure to within 0.5 Å.

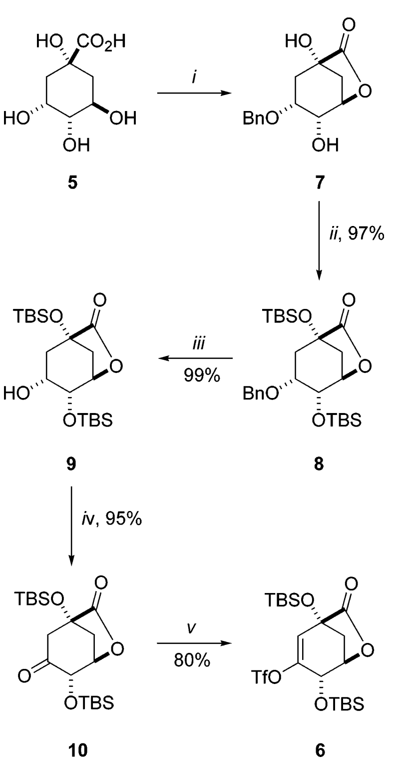


3a X= H (200 μM)
3b X= F (10 μM)
3c (20 μM)

a R= phenyl
b R= (4-F)phenyl
c R= (4-CF$_3$)phenyl
d R= (3-F)phenyl
e R= (3-CF$_3$)phenyl
f R= (3-OH)phenyl
g R= (3-NO$_2$)phenyl
h R= (3-CO$_2$H)phenyl
i R= (3,5-diF)phenyl
j R= thiophen-3-yl
k R= pyridin-3-yl
l R= furan-3-yl

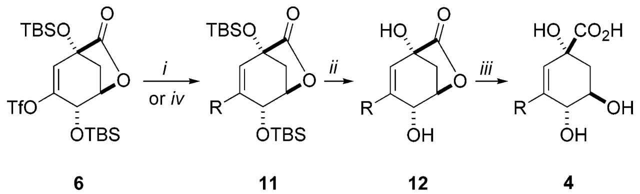
Figure 1. *M. tuberculosis* type II dehydroquinase inhibitors.

Scheme 4[a]



[a] Reagents and conditions: (i) ref 22; (ii) TBSOTf, Py, DCM, 0 °C → room temp; (iii) H_2, $Pd(OH)_2$, MeOH, room temp; (iv) PDC, 4 Å molecular sieves, DCM, room temp; (v) (1) $KN(TMS)_2$, DMF, toluene, −78 °C, (2) triflimide, −78 °C → room temp.

Scheme 5[a]



[a] Reagents and conditions: (i) $(dba)_3Pd_2{\cdot}CHCl_3$, DCM, THF, Et_3N, $ArB(OH)_2$, −78 °C → room temp; (ii) TBAF, THF, 0 °C → room temp; (iii) (1) LiOH, THF, room temp, (2) Amberlite IR-120 (H^+); (iv) (3-Py)$B(OR)_2$, $Pd(PPh_3)_4$, dioxane, aqueous K_3PO_4, Δ.

Table 1. Synthesis of Compounds **11**, **12**, and **4**[a]

		6 → 11		11 → 12		12 → 4	
entry	R	11	yield (%)	12	yield (%)	4	yield (%)
1	phenyl	**11a**	93	**12a**	76	**4a**	84
2	(4-F)phenyl	**11b**	61	**12b**	88	**4b**	89
3	(4-CF_3)phenyl	**11c**	96	**12c**	81	**4c**	92
4	(3-F)phenyl	**11d**	89	**12d**	87	**4d**	99
5	(3-CF_3)phenyl	**11e**	77	**12e**	94	**4e**	98
6	(3-OH)phenyl	**11f**	90	**12f**	60	**4f**	93
7	(3-NO_2)phenyl	**11g**	88	**12g**	79	**4g**	99
8	(3-CO_2R')phenyl	**11h**[a]	62	**12h**[a]	89	**4h**[b]	83
9	(3,5-diF)phenyl	**11i**	77	**12i**	97	**4i**	87
10	3-thiophenyl	**11j**	69	**12j**	82	**4j**	93
11	3-pyridinyl	**11k**	70	**12k**	94	**4k**	96
12	3-furanyl	**11l**	71	**12l**	79	**4l**	98

[a] R′ = Me. [b] R′ = H.

Table 2. Inhibition Results for Assays with *M. tuberculosis* Type II Dehydroquinase[a]

compd	R	K_i (nM)
4a	phenyl	1500
4b	(4-F)phenyl	1800
4c	(4-CF_3)phenyl	17000
4d	(3-F)phenyl	1500
4e	(3-CF_3)phenyl	2125
4f	(3-OH)phenyl	95000
4g	(3-NO_2)phenyl	54
4h	(3-CO_2H)phenyl	150000
4i	(3,5-diF)phenyl	2440
4j	tiophen-3-yl	590
4k	pyridin-3-yl	45000
4l	furan-3-yl	830

[a] K_M value of 40 μM was obtained at the assay conditions.

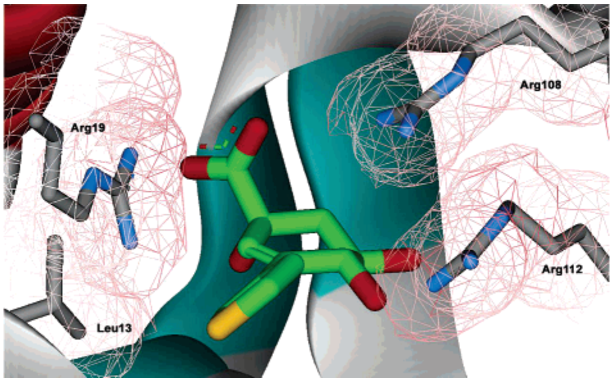


Figure 2. Docking results of the highest score solution of ligand **4j** (green).

All 25 GOLD runs for all ligands showed the carboxyl group binding to the backbone amides of Ile102 and Ser103, and the C-1 hydroxyl binding to His101 and Asn75 as in the enzyme−inhibitor complex. The cyclohexene ring of the inhibitors occupied approximately the same site as **3c** in the crystal structure of the enzyme−inhibitor complex. The predicted binding puts the aromatic ring of the ligands into the pocket formed between the three arginines of the active site, Arg19, Arg108, and Arg112. However, differences were observed in the position of the aromatic ring of the ligands, leading to some differences in the predicted relative binding of the analogues.

The key binding association for the aromatic ring appeared to be its electrostatic interaction with Arg19. The aromatic rings of the inhibitors are located parallel to Arg19, with the exception of pyridine **4k** and thiophene **4j**, which are orientated perpendicularly (Figure 2). This may be due to stronger electrostatic interactions between the heteroatom (N, S) and Arg19 than between the aromatic ring π-system and Arg19. This heteroatom−arginine interaction should be stronger in **4j** than in **4k** because the sulfur still has a free electron pair not implicated in the π-system and may be responsible for the inhibitory potency of the thiophene analogue **4j**.

The docking results of fluoro (**4b**, **4d**, and **4i**) and trifluoromethyl derivatives (**4c**, **4e**) were quite similar, suggesting that these substituents do not introduce significant changes in the π-system of the aromatic ring.

The predicted binding for the most potent inhibitor, the 3-nitrophenyl analogue **4g** (Figure 3), suggests a strong electrostatic interaction between the nitro group and Arg19, which may be responsible for the low K_i value observed.

Conclusions

Suzuki cross-coupling between a vinyl triflate derivative from (−)-quinic acid and diverse arylboronic acids

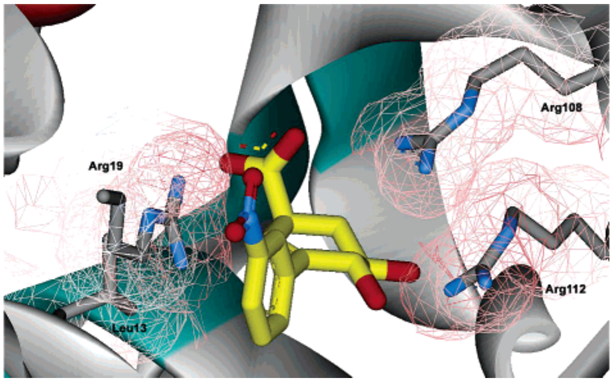


Figure 3. Docking results of the highest score solution of ligand **4g** (yellow).

has been used for the synthesis of 12 5-aryl analogues of the known inhibitor **3a**. These compounds were assayed against *Mycobacterium tuberculosis* type II dehydroquinase and showed competitive inhibition against this enzyme. Nine of them were more potent than the reported inhibitors **3a**, **3b**, and **3c**. The most potent inhibitor, 3-nitrophenyl derivative **4g**, has a K_i of 54 nM, over 180 times more potent than the original 5-fluoro inhibitor **3b** and more than 700 times lower than the K_M of the substrate, making it the most potent known inhibitor against any type II dehydroquinase. Docking studies using GOLD (version 2.2) indicated a key electrostatic binding interaction between the aromatic rings as well as the nitro group in the case of compound **4g** and Arg19, a residue that has been identified as being essential for enzyme activity. These docking studies need to be supported with structural studies of enzyme−inhibitor complexes, which are underway and should be considered for the design of the next generation of inhibitors.

Experimental Section

General Procedures. All starting materials and reagents were commercially available and used without further purification. FT-IR spectra were recorded as NaCl plates or KBr disks. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra (250, 300, and 500 MHz) and ^{13}C NMR spectra (63, 75, and 100 MHz) were measured in deuterated solvents. *J* values are given in hertz. NMR assignments were made by a combination of 1D, COSY, and DEPT-135 experiments. All procedures involving the use of ion-exchange resins were carried out at room temperature and used Mili-Q deionized water. Amberlite IR-120 (H$^+$) (cation exchanger) was washed sequentially with water, 10% NaOH, water, 10% HCl, and finally water before use. The purity of carboxylic acids was analyzed by HPLC and by NMR. HPLC was performed on a preparative (300 mm × 16 mm) Bio-Rad Aminex ion exclusion HPX-87H organic acids column. The eluent used for these columns was 100 mM aqueous formic acid at a flow rate of 0.6 mL min^{-1}.

Dehydroquinase Assay. *M. tuberculosis* type II dehydroquinase was purified as described previously.[28] A concentrated solution (0.7 mg mL^{-1}) was stored in potassium phosphate buffer (50 mM, pH 7.2), DTT (1 mM), and NaCl (150 mM). When required for assays, aliquots of the enzyme stocks were diluted in water and buffer and stored on ice.

Dehydroquinase was assayed in the forward direction by monitoring the increase in the absorbance at 234 nm in the UV spectrum due to the absorbance of the enone−carboxylate chromophore of 3-dehydroshikimic acid (**2**) (ϵ = 12 000 M^{-1} cm^{-1}). Standard assay conditions for type II dehydroquinase were pH 8.2 at 25 °C in Tris/HOAc (50 mM). Each assay was initiated by addition of the substrate. Solutions of 3-dehydroquinic acid (**1**) were calibrated by equilibration with type II dehydroquinase and measurement of the change in the UV absorbance at 234 nm due to the formation of the enone−carboxylate chromophore of 3-dehydroshikimic acid (**2**).

Docking. The receptor and ligands were used as MOL2 files. Each ligand was docked using GOLD (version 2.2) in 25 independent genetic algorithm (GA) runs, and for each of these a maximum number of 100 000 GA operations were performed on a single population of 50 individuals. Operator weights for crossover, mutation, and migration in the entry box were used as default parameters (95, 95, and 10, respectively), as well as the hydrogen bonding (4.0 Å) and van der Waals (2.5 Å) parameters. The position of the active site was introduced, and the radius was set to 15 Å, with the automatic active-site detection on. The "flip ring corners" flag was switched on, while all the other flags were off.

(1*S*,3*R*,4*R*,5*R*)-3-Benciloxy-1,4-di(*tert*-butyldimethylsilyloxy)cyclohexan-1,5-carbolactone (8). To a stirred solution of the diol **7**[22] (1.00 g, 3.79 mmol) in dry DCM (13 mL) and pyridine (1.1 mL, 13.27 mmol) under an inert atmosphere at 0 °C was added *tert*-butyldimethylsilyl trifluorosulfonate (2.6 mL, 11.37 mmol). The resultant solution was stirred at room temperature for 12 h and then diluted with DCM and water. The aqueous layer was acidified with HCl (10%), and the organic phase was separated. The aqueous phase was extracted twice with DCM. All the combined organic extracts were dried (anhydrous Na_2SO_4), filtered, and evaporated. The obtained residue was purified by flash chromatography, eluting with 10% ethyl acetate−hexanes to yield silyl ether **8** (1.81 g, 97%) as a colorless oil. $[\alpha]^{20}_D$ −14° (*c* 1.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.31 (m, 5H), 4.45 (t, 1H, *J* 5.6), 4.42 (s, 2H), 4.11 (t, 1H, *J* 4.6), 3.42 (ddd, 1H, *J* 11.7, 6.2 and 4.1), 2.43 (d, 1H, *J* 11.4), 2.13−1.98 (m, 2H), 1.76 (t, 1H, *J* 11.9), 0.70 (s, 9H), 0.69 (s, 9H), −0.07 (s, 3H), −0.09 (s, 3H), −0.15 (s, 3H) and −0.16 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 176.3, 137.8, 128.3 (2×), 127.7, 127.6 (2×), 75.9, 74.1, 73.7, 71.1, 65.7, 38.1, 37.5, 25.7 (3×), 25.6 (3×), 18.1, 18.0, −2.9 (2×), −4.5, and −5.0.

(1*S*,3*R*,4*R*,5*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-3-hydroxycyclohexan-1,5-carbolactone (9). A suspension of the disilyl ether **8** (270 mg, 0.55 mmol) and 20% palladium hydroxide on carbon (50 mg) in methanol (15 mL) was shaken under hydrogen atmosphere at room temperature for 48 h. The mixture was filtered over Celite, and the residue was washed with methanol. The filtrate and washings were evaporated under reduced pressure to yield a white solid that was purified by flash chromatography, eluting with 10% ethyl acetate−hexanes to yield alcohol **9** (218 mg, 99%) as white needless. Mp 107−108 °C; $[\alpha]^{20}_D$ −1° (*c* 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 4.49 (t, 1H, *J* 5.5), 3.95 (t, 1H, *J* 4.8), 3.75−3.61 (m, 1H), 2.24 (d, 1H, *J* 11.4), 2.08 (m, 2H), 1.87 (d, 1H, *J* 11.6), 1.53 (t, 1H, *J* 12.6), 0.73 (s, 9H), 0.67 (s, 9H), −0.06 (s, 3H), −0.08 (s, 3H), −0.10 (s, 3H), and −0.11 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 175.9, 75.6, 73.6, 67.0, 66.1, 41.4, 37.8, 25.7 (3×), 25.5 (3×), 18.0 (2×), −2.9 (2×), −4.6, and −4.9.

(1*S*,4*S*,5*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-3-oxocyclohexan-1,5-carbolactone (10). To a stirred suspension of the alcohol **9** (1.24 g, 3.09 mmol) and 4 Å activated powder molecular sieves (1.24 g) in dry DCM (31 mL) was added pyridinium dichromate (1.40 g, 3.71 mmol). The resultant suspension was stirred vigorously at room temperature. After 3 h, more 4 Å activated powder molecular sieves (750 mg) were added and the resultant suspension was stirred for an additional 2 h. The reaction mixture was filtered over a plug of Celite and silica gel, and the residue was washed with diethyl ether. The filtrate and the washings were concentrated under reduced pressure. The brown solid obtained was redisolved in hot hexane and treated with activated carbon. The black suspension was filtered over Celite, and the residue was washed with hot hexane. The filtrate and the washings were concentrated and recrystallized to afford the ketone **10** (1.17 g, 95%) as white needless. Mp 50−51 °C (hexanes); $[\alpha]^{20}_D$ −24° (*c* 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 4.51 (dd, 1H, *J* 5.9 and 4.1), 3.81 (br d, 1H, *J* 4.1), 2.74 (d, 1H, *J* 17.6), 2.60 (ddd, 1H, *J* 17.6, 2.7, and 0.9), 2.50 (d, 1H, *J* 12.3), 2.44−2.35 (ddd, 1H, *J* 12.3, 5.9, and 0.9), 0.67 (s, 9H), 0.66 (s, 9H), −0.04 (s, 3H), −0.09 (s, 3H), −0.11 (s, 3H), and −0.15 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 203.2, 175.2, 74.1, 73.1, 71.0, 50.9, 37.0, 25.5 (3×), 25.5 (3×), 18.0, 17.9, −3.1, −3.4, −4.9, and −5.3.

(1*R*,3*R*,4*S*)-1,4-Di(*tert*-butyldimethylsilyloxy)cyclohex-5-en-1,3-carbolactone trifluoromethane Sulfonate (6). To a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene) (3 mL, 1.5 mmol) in dry DMF (1.7 mL) under an inert atmosphere at −78 °C, a solution of the ketone **10** (500 mg, 1.25 mmol) in dry DMF (2.5 mL) and toluene (1.7 mL) was added dropwise. The resultant mixture was stirred for 1 h at this temperature, and a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (735 mg, 1.87 mmol) in dry DMF (1.9 mL) was then added dropwise. The resultant reaction mixture was stirred for 15 h, during which period it was allowed to warm until room temperature. Water and diethyl ether were added, the organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. All the combined organic layers were dried (anhydrous Na$_2$SO$_4$), filtered, and evaporated. The obtained light-yellow oil was purified by flash chromatography (eluent, 50% DCM−hexanes) to afford vinyl triflate **6** (665 mg, 80%) as a colorless oil that solidifies on standing. [α]$^{20}_{\rm D}$ −32° (*c* 0.6, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 6.05 (s, 1H), 4.45 (dd, 1H, *J* 6.6 and 3.7), 4.20 (d, 1H, *J* 3.7), 2.24 (m, 2H), 0.71 (s, 9H), 0.71 (s, 9H), −0.03 (s, 3H), −0.05 (s, 3H), −0.07 (s, 3H), and −0.07 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 173.7, 146.1, 126.1, 118.3 ($J_{\rm CF}$ 318), 74.5, 73.6, 67.3, 36.8, 25.5 (3×), 25.4 (3×), 17.9, 17.8, −3.3 (2×), −5.1 and −5.1; ^{19}F NMR (282 MHz, CDCl$_3$) δ (ppm) −73.7 (s, 3F).

General Procedure of Suzuki Coupling. To a stirred solution of the vinyl triflate **6** (1 equiv) and (dba)$_3$Pd$_2$·CHCl$_3$ (0.075 equiv) in dry DCM under inert atmosphere at −78 °C, 2 equiv of a solution of the boronic acid in dry THF (0.15 M) and 3 equiv of dry triethylamine were added. The dry ice bath was removed, and after 1 h at room temperature more boronic acid (1−1.5 equiv) in dry THF was added to the reaction mixture cooled at −78 °C. The reaction mixture was stirred at room temperature between 14 and 16 h. The solvents were removed under reduced pressure, and the crude residue was purified by flash chromatography.

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-phenylcyclohex-5-en-1,3-carbolactone (11a). Vinyl triflate **6** (50 mg, 0.09 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (7 mg, 7.0 μmol), DCM (0.5 mL), phenylboronic acid (23 mg, 0.19 mmol), THF (1.25 mL), and triethylamine (40 μL, 0.29 mmol) were combined to produce a mixture. After 1 h a solution of phenylboronic acid (11.5 mg, 0.09 mmol) in dry THF (0.6 mL) was added. Chromatographic eluent: DCM−hexanes (50%). **11a** (40 mg, 93%) as a light-orange oil. [α]$^{20}_{\rm D}$ −199° (*c* 1.2, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 7.29−7.16 (m, 5H), 5.97 (d, 1H, *J* 1.8), 4.55−4.50 (m, 2H), 2.41 (d, 1H, *J* 10.7), 2.35−2.27 (m, 1H), 0.87 (s, 9H), 0.65 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), −0.03 (s, 3H), and −0.36 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.6, 139.5, 138.0, 132.9, 128.3 (2×), 128.0, 127.1 (2×), 76.0, 74.9, 67.3, 36.5 (3×), 25.6 (3×), 25.5, 18.0, 17.8, −3.0, −3.1, −4.7, and −5.2.

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(4-fluoro)phenylcyclohex-5-en-1,3-carbolactone (11b). Vinyl triflate **6** (55 mg, 0.10 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (8 mg, 7.5 μmol), DCM (0.4 mL), 4-fluorophenylboronic acid (28 mg, 0.20 mmol), THF (1.4 mL), and triethylamine (42 μL, 0.30 mmol) were combined to produce a mixture. After 1 h a solution of 4-fluorophenylboronic acid (14 mg, 0.10 mmol) in dry THF (0.4 mL) was added. Chromatographic eluent: DCM−hexanes (35%). **11b** (29 mg, 61%) as a colorless oil. [α]$^{20}_{\rm D}$ −37° (*c* 0.6, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 7.52 (ddd, 2H, *J* 9.0, 3.8, and 1.7), 7.29 (t, 2H, *J* 8.9), 6.25 (d, 1H, *J* 1.6), 4.78 (m, 2H), 2.60 (d, 1H, *J* 10.8), 2.52 (ddd, 1H, *J* 10.8, 5.4, and 1.4), 1.02 (s, 9H), 0.81 (s, 9H), 0.27 (s, 3H), 0.25 (s, 3H), 0.10 (s, 3H), and −0.20 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.5, 162.6 ($J_{\rm CF}$ 246), 138.5, 134.0, 133.2, 128.8 (2×, $J_{\rm CF}$ 8), 115.2 (2×, $J_{\rm CF}$ 21), 75.9, 74.8, 67.5, 36.4, 25.6 (3×), 25.5 (3×), 18.0, 17.8, −3.0, −3.0, −4.6, and −5.1; ^{19}F NMR (282 MHz, CDCl$_3$) δ (ppm) −118.2 (m, 1F).

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(4-trifluoromethyl)phenylcyclohex-5-en-1,3-carbolactone (11c). Vinyl triflate **6** (61 mg, 0.12 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (9 mg, 8.6 μmol), DCM (0.5 mL), 4-trifluoromethylphenylboronic acid (44 mg, 0.23 mmol), THF (1 mL), and triethylamine (50 μL, 0.35 mmol) were combined to produce a mixture. After 1 h a solution of 4-trifluoromethylphenylboronic acid (23 mg, 0.12 mmol) in dry THF (0.5 mL) was added. Chromatographic eluent: DCM−hexanes (35%). **11c** (58 mg, 96%) as a colorless oil. [α]$^{20}_{\rm D}$ −159° (*c* 1.3, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 7.60 (d, 2H, *J* 8.4), 7.39 (d, 2H, *J* 8.4), 6.08 (d, 1H, *J* 1.5), 4.52 (m, 2H), 2.32 (m, 2H), 0.75 (s, 9H), 0.52 (s, 9H), 0.00 (s, 3H), −0.03 (s, 3H), −0.17 (s, 3H), and −0.49 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.3, 141.6, 138.4, 134.7, 130.2 ($J_{\rm CF}$ 32), 127.5 (2×), 125.2 (2×, $J_{\rm CF}$ 4), 124.0 ($J_{\rm CF}$ 270), 75.8, 74.9, 67.3, 36.4, 25.6 (3×), 25.4 (3×), 18.0, 17.8, −3.0, −3.1, −4.6, and −5.2; ^{19}F NMR (282 MHz, CDCl$_3$) δ (ppm) −62.7 (s, 3F).

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(3-fluoro)phenylcyclohex-5-en-1,3-carbolactone (11d). Vinyl triflate **6** (50 mg, 0.09 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (7 mg, 7.0 μmol), DCM (0.5 mL), 3-fluorophenylboronic acid (26 mg, 0.19 mmol), THF (1.25 mL), and triethylamine (40 μL, 0.29 mmol) were combined to produce a mixture. After 1 h a solution of 3-fluorophenylboronic acid (14 mg, 0.09 mmol) in dry THF (0.6 mL) was added. Chromatographic eluent: DCM−hexanes (50%). **11d** (40 mg, 89%) as a colorless oil. [α]$^{20}_{\rm D}$ −197° (*c* 1.3, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 7.27−7.20 (m, 1H), 6.99−6.90 (m, 3H), 6.00 (d, 1H, *J* 1.6), 4.53 (m, 2H), 2.37 (d, 1H, *J* 10.7), 2.33 (ddd, 1H, *J* 10.7, 5.1, and 1.6), 0.87 (s, 9H), 0.66 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), −0.01 (s, 3H), and −0.3 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.4, 162.6 ($J_{\rm CF}$ 245), 140.1 ($J_{\rm CF}$ 8), 138.3 ($J_{\rm CF}$ 2), 133.9, 129.8 ($J_{\rm CF}$ 8), 122.7 ($J_{\rm CF}$ 3), 114.9 ($J_{\rm CF}$ 21), 114.2 ($J_{\rm CF}$ 22), 75.8, 74.8, 67.3, 36.4, 25.6 (3×), 25.5 (3×), 18.0, 17.8, −3.0, −3.0, −4.6, and −5.1; ^{19}F NMR (282 MHz, CDCl$_3$) δ (ppm) −113.7 (m, 1F).

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(3-trifluoromethyl)phenylcyclohex-5-en-1,3-carbolactone (11e). Vinyl triflate **6** (133 mg, 0.25 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (24 mg, 23 μmol), DCM (1.1 mL), 3-trifluoromethylphenylboronic acid (95 mg, 0.50 mmol), THF (3.3 mL), and triethylamine (105 μL, 0.76 mmol) were combined to produce a mixture. After 1 h a solution of 3-trifluoromethylphenylboronic acid (71 mg, 0.38 mmol) in dry THF (1.6 mL) was added. Chromatographic eluent: DCM−hexanes [(1) 20%, (2) 35%]. **11e** (102 mg, 77%) as a pale-yellow oil. [α]$^{20}_{\rm D}$ −135° (*c* 1.3, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 7.59−7.46 (m, 4H), 6.12 (d, 1H, *J* 1.5), 4.63 (m, 2H), 2.52−2.40 (m, 2H), 0.95 (s, 9H), 0.73 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H), 0.06 (s, 3H), and −0.25 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.3, 138.8, 138.2, 134.6, 130.7 ($J_{\rm CF}$ 32), 130.6, 128.9, 124.8 ($J_{\rm CF}$ 4), 124.0 ($J_{\rm CF}$ 4), 123.9 ($J_{\rm CF}$ 271), 75.8, 74.9, 67.4, 36.4, 25.6 (3×), 25.4 (3×), 18.0, 17.7, −3.0, −3.1, −4.6, and −5.4; ^{19}F NMR (282 MHz, CDCl$_3$) δ (ppm) −63.1 (s, 3F).

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(3-hydroxy)phenylcyclohex-5-en-1,3-carbolactone (11f). Vinyl triflate **6** (50 mg, 0.09 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (7 mg, 7 μmol), DCM (0.5 mL), 3-hydroxyphenylboronic acid (26 mg, 0.19 mmol), THF (1.3 mL), and triethylamine (40 μL, 0.29 mmol) were combined to produce a mixture. After 1 h a solution of 3-hydroxyphenylboronic acid (13 mg, 0.09 mmol) in dry THF (0.6 mL) was added. Chromatographic eluent: diethyl ether−hexanes [(1) 25%, (2) 50%]. **11f** (40 mg, 90%) as a colorless oil. [α]$^{20}_{\rm D}$ −88° (*c* 1.0, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 7.12 (td, 1H, *J* 7.7 and 0.8), 6.75−6.70 (m, 3H), 6.00 (d, 1H, *J* 1.7), 4.60−4.50 (m, 2H), 2.49−2.28 (m, 2H), 0.86 (s, 9H), 0.68 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.00 (s, 3H), and −0.68 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 176.2, 155.7, 139.4, 139.3, 132.7, 129.5, 119.4, 115.1, 114.1, 76.2, 74.9, 67.2, 36.5, 25.6 (3×), 25.5 (3×), 18.0, 17.8, −2.9, −3.0, −4.7, and −5.1.

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(3-nitro)phenylcyclohex-5-en-1,3-carbolactone (11g). Vinyl triflate **6** (168 mg, 0.32 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (24 mg, 24 μmol), DCM (1.4 mL), 3-nitrophenylboronic acid (107 mg, 0.64 mmol), THF (4.1 mL), and triethylamine (140 μL, 0.97 mmol) were combined to produce a mixture. Chromatographic eluent: DCM−hexanes (35%). **11g** (142 mg, 88%) as a pale-yellow oil. [α]$^{20}_{D}$ −141° (*c* 1.1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.15 (d, 2H, *J* 5.5), 7.68−7.49 (m, 2H), 6.19 (s, 1H), 4.64 (m, 2H), 2.48 (m, 2H), 0.95 (s, 9H), 0.73 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), 0.10 (s, 3H), and −0.18 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 174.8, 148.0, 139.4, 137.2, 135.4, 133.0, 129.4, 122.8, 122.0, 75.7, 74.9, 67.3, 36.4, 25.7 (3×), 25.5 (3×), 18.1, 17.9, −2.9, −2.9, −4.3, and −4.9.

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(3-carboxymethyl)phenylcyclohex-5-en-1,3-carbolactone (11h). Vinyl triflate **6** (50 mg, 0.09 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (7 mg, 7.0 μmol), DCM (0.5 mL), 3-carboxymethylphenylboronic acid (51 mg, 0.28 mmol), THF (1.9 mL), triethylamine (40 μL, 0.29 mmol). Chromatographic eluent: DCM−hexanes [(1) 35%, (2) 50%]. **11h** (30 mg, 62%) as a light-yellow oil. [α]$^{20}_{D}$ −150° (*c* 1.3, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 8.00−7.96 (m, 2H), 7.48 (dt, 1H, *J* 8.0 and 1.5), 7.41 (dd, 1H, *J* 8.0 and 7.8), 6.12 (d, 1H, *J* 1.5), 4.64 (m, 2H), 3.92 (s, 3H), 2.51 (d, 1H, *J* 10.8), 2.42 (ddd, 1H, *J* 10.8, 5.2, and 1.5), 0.95 (s, 9H), 0.73 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H), 0.07 (s, 3H), and −0.25 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.4, 166.7, 138.4, 138.1, 134.0, 131.6, 130.2, 129.2, 128.5, 128.2, 75.9, 74.9, 67.2, 52.2, 36.4, 25.6 (3×), 25.5 (3×), 18.0, 17.8, −3.0, −3.1, −4.6, and −5.2.

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(3,5-difluoro)phenylcyclohex-5-en-1,3-carbolactone (11i). Vinyl triflate **6** (139 mg, 0.26 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (20 mg, 20 μmol), DCM (1.1 mL), 3,5-difluorophenylboronic acid (82 mg, 0.52 mmol), THF (3.4 mL), and triethylamine (110 μL, 0.79 mmol) were combined to produce a mixture. Chromatographic eluent: DCM−hexanes (35%). **11i** (100 mg, 77%) as a colorless oil. [α]$^{20}_{D}$ −170° (*c* 1.1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.85−6.71 (m, 3H), 6.12 (d, 1H, *J* 1.5), 4.61 (m, 1H), 4.54 (d, 1H, *J* 3.3), 2.45 (m, 2H), 0.96 (s, 9H), 0.78 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), 0.10 (s, 3H), and −0.13 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 174.9, 162.7 (2×, J_{CF} 247 and 13), 141.1 (J_{CF} 9), 137.4, 134.7, 110.1 (2×, J_{CF} 21), 103.4 (J_{CF} 21), 75.7, 74.8, 67.3, 36.4, 25.7 (3×), 25.5 (3×), 18.1, 17.9, −2.8, −2.9, −4.3, and −4.9; ^{19}F NMR (282 MHz, CDCl$_3$) δ (ppm) −73.9 (s, 2F).

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(thiophen-3-yl)cyclohex-5-en-1,3-carbolactone (11j). Vinyl triflate **6** (50 mg, 94 μmol), (dba)$_3$Pd$_2$·CHCl$_3$ (7 mg, 7 μmol), DCM (0.5 mL), 3-thiopheneboronic acid (24 mg, 0.19 mmol), THF (1.3 mL), and triethylamine (40 μL, 0.29 mmol) were combined to produce a mixture. After 1 h a solution of 3-thiophene boronic acid (12 mg, 94 μmol) in dry THF (0.6 mL) was added. Chromatographic eluent: DCM−hexanes (50%). **11j** (30 mg, 69%) as a white amorphous solid. Mp 98−100 °C; [α]$^{20}_{D}$ −186° (*c* 1.1, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 7.28 (dd, 1H, *J* 5.0 and 3.0), 7.20 (dd, 1H, *J* 3.0, and 1.3), 7.08 (dd, 1H, *J* 5.0, and 1.3), 6.14 (d, 1H, *J* 1.9), 4.61 (dd, 1H, *J* 5.7, and 3.5), 4.56 (d, 1H, *J* 3.5), 2.50 (d, 1H, *J* 10.6), 2.40 (ddd, 1H, *J* 10.6, 5.7, and 1.9), 0.94 (s, 9H), 0.80 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.12 (s, 3H), and −0.05 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.5, 138.9, 134.1, 132.1, 126.2, 125.7, 122.1, 75.9, 74.8, 67.6, 36.6, 25.6 (6×), 18.0, 17.9, −3.0 (2×), −4.3, and −4.8.

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(pyridine-3-yl)cyclohex-5-en-1,3-carbolactone (11k). To a stirred solution of the vinyl triflate **6** (50 mg, 0.09 mmol) in dioxane (0.5 mL) was added Pd(PPh$_3$)$_4$ (3 mg, 2.35 μmol), 3-(1,3,2)-dioxaborinan-2-ylpyridine (17 mg, 0.10 mmol), and 0.2 mL of an aqueous solution of K$_3$PO$_4$ (0.8 M). The resultant reaction mixture was heated under reflux for 2 h. After the mixture was cooled to room temperature, DCM was added and the organic layer was separated. The aqueous phase was extracted with DCM (2×). The combined organic extracts were dried (anhydrous Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The crude reaction was purified by flash chromatography, eluting with diethyl ether−hexanes [(1) 25%, (2) 50%] to afford pyridine **11k** (30 mg, 70%) as pale-yellow needles. Mp 78−80 °C; [α]$^{20}_{D}$ −189° (*c* 1.0, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 8.84 (m, 2H), 7.87 (dt, 1H, *J* 8.0 and 0.5), 7.55 (m, 1H), 6.41 (d, 1H, *J* 1.1), 4.89 (m, 2H), 2.75 (m, 2H), 1.23 (s, 9H), 1.02 (s, 9H), 0.50 (s, 3H), 0.48 (s, 3H), 0.35 (s, 3H), and 0.06 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.2, 149.2, 148.3, 136.4, 134.9, 134.4, 133.6, 123.0, 75.7, 74.8, 67.2, 36.3, 25.6 (3×), 25.4 (3×), 18.0, 17.7, −3.0, −3.1, −4.6, and −5.1.

(1*R*,3*R*,4*R*)-1,4-Di(*tert*-butyldimethylsilyloxy)-5-(furan-3-yl)cyclohex-5-en-1,3-carbolactone (11l). Vinyl triflate **6** (150 mg, 0.28 mmol), (dba)$_3$Pd$_2$·CHCl$_3$ (22 mg, 21 μmol), DCM (1.5 mL), 3-furaneboronic acid (63 mg, 0.56 mmol), THF (3.8 mL), and triethylamine (120 μL, 0.86 mmol) were combined to produce a mixture. After 1 h a solution of 3-furaneboronic acid (32 mg, 0.28 mmol) in dry THF (1.9 mL) was added. Chromatographic eluent: DCM−hexanes (35%). **11l** (90 mg, 71%) as a white amorphous solid. Mp 97−99 °C; [α]$^{20}_{D}$ −166° (*c* 1.1, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ (ppm) 7.46 (br s, 1H), 7.36 (t, 1H, *J* 1.75), 6.42 (dd, 1H, *J* 1.75 and 0.75), 6.07 (d, 1H, *J* 1.75), 4.60 (dd, 1H, *J* 5.75 and 3.25), 4.41 (d, 1H, *J* 3.25), 2.46 (d, 1H, *J* 10.75), 2.38 (ddd, 1H, *J* 10.75, 5.75, and 1.75), 0.94 (s, 9H), 0.86 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), and 0.08 (s, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 175.4, 143.1, 139.8, 131.4, 130.5, 123.3, 108.7, 75.8, 74.9, 67.6, 36.8, 25.6 (6×), 18.0, 17.9, −3.0 (2×), −4.1, and −4.6.

General Procedure for TBS Deprotection. To a stirred solution of the silyl ether **11** (1 equiv) in dry THF (75 mM) under argon at 0 °C was added tetrabutylammonium fluoride (2.2−2.6 equiv, ca. 1.0 M in THF). After the mixture was stirred for 30 min, dilute HCl was added and the organic layer was extracted with ethyl acetate (×3). The combined organic extracts were dried (anhydrous Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The crude reaction was purified by flash chromatography.

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-phenylcyclohex-5-en-1,3-carbolactone (12a). The reaction was carried out as described above. Silyl ether **11a** (110 mg, 0.24 mmol), tetrabutylammonium fluoride (0.53 mL, 0.53 mmol), and THF (3.4 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (75%). **12a** (42 mg, 76%) as a light-orange oil. [α]$^{20}_{D}$ −257° (*c* 1.1, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.48 (d, 2H, *J* 7.5), 7.31 (m, 3H), 6.28 (s, 1H), 4.70−4.66 (m, 2H), and 2.39 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.5, 139.8, 138.2, 131.8, 129.6 (2×), 129.3, 127.3 (2×), 78.0, 74.3, 66.4, and 36.8.

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(4-fluoro)phenylcyclohex-5-en-1,3-carbolactone (12b). Silyl ether **11b** (156 mg, 0.33 mmol), tetrabutylammonium fluoride (0.86 mL, 0.86 mmol), and THF (4.7 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (60%). **12b** (72 mg, 88%) as colorless oil. [α]$^{20}_{D}$ −237° (*c* 1.1, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.55 (m, 2H), 7.07 (m, 2H), 6.29 (s, 1H), 4.74 (dd, 1H, *J* 6.3, and 3.3), 4.65 (d, 1H, *J* 3.3), and 2.41 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.5, 164.1 (J_{CF} 245), 138.7, 134.5, 131.8, 129.3 (2×, J_{CF} 8), 116.2 (2×, J_{CF} 22), 77.9, 74.3, 66.5, and 36.8; ^{19}F NMR (282 MHz, CD$_3$OD) δ (ppm) −116.2 (m, 1F).

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(4-trifluoromethyl)phenylcyclohex-5-en-1,3-carbolactone (12c). Silyl ether **11** (174 mg, 0.33 mmol), tetrabutylammonium fluoride (0.86 mL, 0.86 mmol), and THF (4.7 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexane (60%). **12c** (80 mg, 81%) as pale-yellow needles. Mp 133−134 °C; [α]$^{20}_{D}$ −198° (*c* 1.2, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.70 (m, 4H), 6.48 (s, 1H), 4.78 (dd, 1H, *J* 6.2 and 3.2), 4.73 (d, 1H, *J* 3.2), and 2.45 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.2, 142.1, 138.6, 134.2, 131.0 (J_{CF} 32), 128.0 (2×), 126.4 (2×, J_{CF} 4), 125.6 (J_{CF} 262), 77.9, 74.4, 66.6, and 36.7; ^{19}F NMR (282 MHz, CD$_3$OD) δ (ppm) −64.5 (s, 3F).

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(3-fluoro)phenylcyclohex-5-en-1,3-carbolactone (12d). Silyl ether **11d** (88 mg, 0.18 mmol), tetrabutylammonium fluoride (0.41 mL, 0.41 mmol), and THF (2.6 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (75%). **12d** (40 mg, 87%) as a white solid. $[\alpha]^{20}_{D}$ −275° (*c* 1.0, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.50−7.28 (m, 3H), 7.15−7.02 (m, 1H), 6.48 (s, 1H), 4.75 (dd, 1H, *J* 6.3 and 3.4), 4.62 (d, 1H, *J* 3.4), and 2.46 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.3, 164.4 (J_{CF} 242), 140.8 (J_{CF} 8), 138.7, 133.1, 131.3 (J_{CF} 8), 123.2 (J_{CF} 3), 115.9 (J_{CF} 21), 114.2 (J_{CF} 23), 77.9, 74.3, 66.4, and 36.8; ^{19}F NMR (282 MHz, CD$_3$OD) δ (ppm) −115.6 (m, 1F).

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(3-trifluoromethyl)phenylcyclohex-5-en-1,3-carbolactone (12e). Silyl ether **11e** (137 mg, 0.26 mmol), tetrabutylammonium fluoride (0.68 mL, 0.68 mmol), and THF (3.7 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (60%). **12e** (73 mg, 94%) as pale-yellow needles. Mp 142−145 °C; $[\alpha]^{20}_{D}$ −212° (*c* 1.0, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.80 (m, 2H), 7.56 (m, 2H), 6.43 (s, 1H), 4.76 (dd, 1H, *J* 6.3 and 3.4), 4.70 (d, 1H, *J* 3.4), and 2.44 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.2, 139.4, 138.6, 133.7, 131.9 (J_{CF} 32), 131.1 (J_{CF} 1), 130.4, 125.8 (J_{CF} 4), 125.6 (J_{CF} 270), 124.1 (J_{CF} 4), 77.9, 74.3, 66.5, and 36.8; ^{19}F NMR (282 MHz, CD$_3$OD) δ (ppm) −64.5 (s, 3F).

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(3-hydroxy)phenylcyclohex-5-en-1,3-carbolactone (12f). Silyl ether **11f** (130 mg, 0.27 mmol), tetrabutylammonium fluoride (0.6 mL, 0.60 mmol), and THF (4 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (75%). **12f** (41 mg, 60%) as a colorless oil. $[\alpha]^{20}_{D}$ −219° (*c* 1.1, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.30 (br d, 1H, *J* 2.3), 7.15 (t, 1H, *J* 7.8), 6.97 (m, 2H), 6.95 (ddd, 1H, *J* 7.8, 2.3, and 0.9), 6.25 (s, 1H), 4.69 (m, 1H), 4.54 (d, 1H, *J* 3.3), and 2.42 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 179.0, 159.0, 140.2, 140.1, 132.1, 131.0, 119.1, 116.8, 114.6, 78.4, 74.7, 66.9, and 37.2.

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(3-nitro)phenylcyclohex-5-en-1,3-carbolactone (12g). Silyl ether **11g** (148 mg, 0.29 mmol), tetrabutylammonium fluoride (0.62 mL, 0.62 mmol), and THF (4 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (60%). **12g** (63 mg, 79%) as pale-yellow amorphous solid. Mp 142−148 °C; $[\alpha]^{20}_{D}$ −179° (*c* 1.2, CH$_3$OH); ^{1}H NMR (300 MHz, CD$_3$OD) δ (ppm) 8.41 (t, 1H, *J* 2.0), 8.17 (ddd, 1H, *J* 8.0, 2.0, and 0.9), 7.94 (ddd, 1H, *J* 8.0, 2.0 and 0.9), 7.60 (t, 1H, *J* 8.0), 6.52 (s, 1H), 4.78 (dd, 1H, *J* 6.0 and 3.6), 4.73 (d, 1H, *J* 3.6), and 2.46 (m, 2H); ^{13}C NMR (75 MHz, CD$_3$OD) δ (ppm) 177.8, 149.7, 140.0, 137.8, 134.4, 133.3, 130.7, 123.7, 122.1, 77.8, 74.3, 66.5, and 36.8.

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(3-carboxymethyl)phenylcyclohex-5-en-1,3-carbolactone (12h). Silyl ether **11h** (120 mg, 0.23 mmol), tetrabutylammonium fluoride (0.50 mL, 0.50 mmol), and THF (3.3 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (75%). **12h** (60 mg, 89%) as a colorless oil. $[\alpha]^{20}_{D}$ −201° (*c* 1.1, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 8.12 (t, 1H, *J* 1.6), 7.88 (dt, 1H, *J* 7.8, and 1.2), 7.72 (dt, 1H, *J* 7.8 and 1.2), 7.41 (t, 1H, *J* 7.8), 6.37 (s, 1H), 4.73 (dd, 1H, *J* 6.2 and 3.2), 4.67 (d, 1H, *J* 3.2), 3.86 (s, 3H), and 2.40 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.4, 168.3, 138.9, 138.7, 133.1, 132.0, 131.6, 130.2, 129.9, 128.4, 77.9, 74.4, 66.4, 52.8, and 36.8.

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(3,4-difluoro)phenylcyclohex-5-en-1,3-carbolactone (12i). Silyl ether **11i** (142 mg, 0.29 mmol), tetrabutylammonium fluoride (0.75 mL, 0.75 mmol), and THF (4.1 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (60%). **12i** (76 mg, 97%) as a pale-yellow oil. $[\alpha]^{20}_{D}$ −185° (*c* 1.1, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.16 (m, 2H), 6.88 (tt, 1H, *J* 9.0 and 2.3), 6.44 (s, 1H), 4.74 (dd, 1H, *J* 6.1 and 3.4), 4.62 (d, 1H, *J* 3.4), and 2.42 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.1, 164.5 (2×, J_{CF} 245 and 13), 142.0 (J_{CF} 10), 137.9 (J_{CF} 3), 134.3, 110.4 (J_{CF} 17), 110.3 (J_{CF} 17), 104.2 (J_{CF} 26), 77.8, 74.3, 66.4, and 36.7; ^{19}F NMR (282 MHz, CD$_3$OD) δ (ppm) −112.1 (t, 2F, *J* 8.7).

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(thiophen-3-yl)cyclohex-5-en-1,3-carbolactone (12j). Silyl ether **11j** (120 mg, 0.26 mmol), tetrabutylammonium fluoride (0.6 mL, 0.60 mmol), and THF (3.7 mL) were combined to produce a mixture. Chromatographic eluent: ethyl acetate−hexanes (60%). **12j** (50 mg, 82%) as amorphous white solid. Mp 147−149 °C; $[\alpha]^{20}_{D}$ −261° (*c* 1.0, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.69 (dd, 1H, *J* 2.9 and 1.3), 7.40 (dd, 1H, *J* 2.9 and 5.1), 7.32 (dd, 1H, *J* 1.3 and 5.1), 6.42 (d, 1H, *J* 1.3), 4.75 (dt, 1H, *J* 3.3 and 1.3), 4.58 (d, 1H, *J* 3.3), and 2.45 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.6, 139.7, 134.8, 130.4, 126.7, 126.4, 123.4, 78.0, 74.2, 67.1, and 37.2.

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(pyridine-3-yl)cyclohex-5-en-1,3-carbolactone (12k). Silyl ether **11k** (126 mg, 0.27 mmol), tetrabutylammonium fluoride (0.6 mL, 0.60 mmol), and THF (3.9 mL) were combined to produce a mixture. Chromatographic eluent: acetone. **12k** (60 mg, 94%) as white needles. Mp 44−46 °C; $[\alpha]^{20}_{D}$ −213° (*c* 1.0, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 8.64 (m, 1H), 8.38 (dd, 1H, *J* 1.6 and 4.7), 7.93 (ddd, 1H, *J* 2.2, 1.6, and 8.0), 7.36 (dd, 1H, *J* 4.7 and 8.0), 6.40 (s, 1H), 4.70 (m, 1H), 4.63 (d, 1H, *J* 3.2), and 2.38 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.1, 149.4, 148.0, 136.8, 136.0, 134.8, 134.2, 125.2, 77.8, 74.4, 66.3, and 36.8.

(1*R*,3*R*,4*R*)-1,4-Dihydroxy-5-(furan-3-yl)cyclohex-5-en-1,3-carbolactone (12l). Silyl ether **11l** (150 mg, 0.33 mmol), tetrabutylammonium fluoride (0.7 mL, 0.73 mmol), and THF (4.8 mL) were combined to produce a mixture. Chromatographic eluent: (1) diehyl ether−hexanes (75%), (2) diethyl ether. **12l** (58 mg, 79%) as colorless oil that solidifies on standing. $[\alpha]^{20}_{D}$ −240° (*c* 1.1, CH$_3$OH); ^{1}H NMR (250 MHz, CD$_3$OD) δ (ppm) 7.45 (s, 1H), 7.46 (t, 1H, *J* 1.75), 6.62 (dd, 1H, *J* 1.75 and 0.75), 6.20 (s, 1H), 4.69 (m, 1H), 4.38 (d, 1H, *J* 3.25), and 2.39 (m, 2H); ^{13}C NMR (63 MHz, CD$_3$OD) δ (ppm) 178.7, 144.6, 141.9, 132.1, 129.7, 124.5, 108.8, 78.1, 74.2, 67.3, and 37.6.

General Procedure of Lactone Hydrolysis. A solution of the lactone **12** (1 equiv) in THF (0.1 M) and aqueous lithium hydroxide (2.5 equiv, 0.5 M) was stirred at room temperature for 30 min. Water was added, the THF was removed under reduced pressure, and the resultant aqueous solution was washed with diethyl ether (×2). The aqueous extract was treated with Amberlite IR-120 until pH 6 was attained. The resin was filtered and washed with water. The filtrate and the washings were lyophilized.

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-phenylcyclohex-5-en-1-carboxylic Acid (4a). Lactone **12a** (42 mg, 0.18 mmol), THF (1.6 mL), and aqueous lithium hydroxide (0.9 mL) were combined to produce a mixture. **4a** (40 mg, 88%) as an amorphous white solid. Retention time: 33 min. Mp 147−149 °C; $[\alpha]^{20}_{D}$ −121° (*c* 1.1, H$_2$O); ^{1}H NMR (400 MHz, D$_2$O) δ (ppm) 7.3 (m, 5H), 5.78 (s, 1H), 4.51 (dd, 1H, *J* 7.6 and 1.6), 3.95 (ddd, 1H, *J* 11.2, 7.6, and 3.8), 2.16 (dd, 1H, *J* 13.4 and 11.2), and 2.05 (dd, 1H, *J* 13.4 and 3.8); ^{13}C NMR (100 MHz, D$_2$O) δ (ppm) 181.1, 147.0, 141.0, 131.5 (2×), 131.2, 130.1 (2×), 128.8, 76.1, 74.8, 72.6, and 41.3.

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(4-fluoro)phenylcyclohex-5-en-1-carboxylic Acid (4b). Lactone **12b** (73 mg, 0.29 mmol), THF (2.6 mL), and aqueous lithium hydroxide (1.5 mL) were combined to produce a mixture. **4b** (69 mg, 89%) as a white amorphous solid. Retention time: 33 min. Mp 118−122 °C; $[\alpha]^{20}_{D}$ −69° (*c* 1.2, CH$_3$OH); ^{1}H NMR (300 MHz, D$_2$O) δ (ppm) 7.25 (dd, 2H, *J* 7.8 and 5.7), 6.99 (dd, 2H, *J* 8.4 and 8.7), 5.72 (s, 1H), 4.44 (d, 1H, *J* 7.3), 3.92 (m, 1H), and 2.09 (m, 2H); ^{13}C NMR (75 MHz, D$_2$O) δ (ppm) 178.1, 162.5 (J_{CF} 243), 143.4, 134.3 (J_{CF} 3), 129.1 (2×, J_{CF} 9), 125.8, 115.3 (2×, J_{CF} 21), 73.2, 72.0, 69.7, and 38.4; ^{19}F NMR (282 MHz, D$_2$O) δ (ppm) −115.2 (m, 1F).

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(4-trifluoromethyl)phenylcyclohex-5-en-1-carboxylic Acid (4c). Lactone **12c** (74 mg, 0.25 mmol), THF (2.3 mL), and aqueous lithium hydroxide (1.3 mL). **4c** (73 mg, 92%) as a white amorphous solid. Retention time: 50 min. Mp 117−120 °C; $[\alpha]^{20}_{D}$ −89° (*c* 1.0, CH$_3$OH); ^{1}H NMR (250 MHz, D$_2$O) δ (ppm) 7.44 (d, 2H, J 8.2), 7.27 (d, 2H, J 8.2), 5.70 (s, 1H), 4.39 (d, 1H, J 7.4), 3.84 (m, 1H), and 2.01 (m, 2H); ^{13}C NMR (63 MHz, D$_2$O) δ (ppm) 178.0, 143.5, 142.1, 129.5 (J_{CF} 32), 127.9 (2×), 127.4, 125.6 (2×, J_{CF} 3), 124.5 (J_{CF} 270), 73.3, 72.1, 69.8, and 38.6; ^{19}F NMR (282 MHz, D$_2$O) δ (ppm) −62.7 (s, 3F).

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(3-fluoro)phenylcyclohex-5-en-1-carboxylic Acid (4d). Lactone **12d** (40 mg, 0.16 mmol), THF (1.5 mL), and aqueous lithium hydroxide (0.8 mL) were combined to produce a mixture. **4d** (42 mg, 99%) as a white amorphous solid. Retention time: 31 min. Mp 117−120 °C; $[\alpha]^{20}_{D}$ −81° (c 1.1, H$_2$O); ^{1}H NMR (300 MHz, D$_2$O) δ (ppm) 7.28 (m, 1H), 7.11−6.95 (m, 3H), 5.81 (s, 1H), 4.46 (d, 1H, J 7.3), 3.93 (ddd, 1H, J 11.1, 7.3 and 3.8), 2.13 (dd, 1H, J 11.1 and 13.5), 2.03 (dd, 1H, J 13.5 and 3.5); ^{13}C NMR (75 MHz, D$_2$O) δ (ppm) 178.4, 162.6 (J_{CF} 241), 143.0, 140.6 (J_{CF} 8), 130.3 (J_{CF} 9), 126.9, 123.2 (J_{CF} 3), 114.9 (J 21), 114.1 (J 22), 73.2, 71.9, 69.7, and 38.4; ^{19}F NMR (282 MHz, D$_2$O) δ (ppm) −114.5 (m, 1F).

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(3-trifluoromethyl)phenylcyclohex-5-en-1-carboxylic Acid (4e). Lactone **12e** (46 mg, 0.15 mmol), THF (1.5 mL), and aqueous lithium hydroxide (0.76 mL) were combined to produce a mixture. **4e** (47 mg, 98%) as a beige amorphous solid. Retention time: 42 min. Mp 122−125 °C; $[\alpha]^{20}_{D}$ −41° (c 1.0, CH$_3$OH); ^{1}H NMR (300 MHz, D$_2$O) δ (ppm) 7.50 (m, 4H), 5.86 (s, 1H), 4.51 (dd, 1H, J 7.8 and 1.5), 3.95 (ddd, 1H, J 11.1, 7.8, and 4.2), and 2.09 (m, 2H); ^{13}C NMR (75 MHz, D$_2$O) δ (ppm) 177.9, 143.2, 139.0, 131.0, 130.1 (J_{CF} 32), 129.2, 127.0, 124.9 (J_{CF} 4), 124.3 (J_{CF} 270), 124.0 (J_{CF} 4), 73.1, 71.9, 69.6, and 38.5; ^{19}F NMR (282 MHz, D$_2$O) δ (ppm) −62.8 (s, 3F).

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(3-hydroxy)phenylcyclohex-5-en-1-carboxylic Acid (4f). Lactone **12f** (40 mg, 0.16 mmol), THF (1.5 mL), and aqueous lithium hydroxide (0.8 mL) were combined to produce a mixture. **4f** (40 mg, 93%) as a white amorphous solid. Retention time: 21 min. Mp 120−122 °C; $[\alpha]^{20}_{D}$ −116° (c 1.2, H$_2$O); ^{1}H NMR (500 MHz, D$_2$O) δ (ppm) 7.21 (t, 1H, J 8.0), 6.91 (d, 1H, J 7.5), 6.83 (t, 1H, J 2.0), 6.78 (dd, 1H, J 8.0 and 2.5), 5.79 (s, 1H), 4.50 (dd, 1H, J 7.0 and 1.0), 3.97 (ddd, 1H, J 11.0, 7.0, and 3.5), 2.17 (dd, 1H, J 13.5 and 11.0), and 12.07 (dd, 1H, J 13.5 and 4.0); ^{13}C NMR (100 MHz, D$_2$O) δ (ppm) 182.2, 158.4, 145.9, 143.1, 132.9, 129.8, 122.3, 118.0, 117.0, 76.4, 74.7, 72.8, and 41.2.

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(3-nitro)phenylcyclohex-5-en-1-carboxylic Acid (4g). Lactone **12g** (61 mg, 0.22 mmol), THF (2 mL), and aqueous lithium hydroxide (1.1 mL) were combined to produce a mixture. **4g** (64 mg, 99%) as a pale-beige amorphous solid. Retention time: 37 min. Mp 138−140 °C; $[\alpha]^{20}_{D}$ −62.5° (c 1.3, CH$_3$OH); ^{1}H NMR (250 MHz, D$_2$O) δ (ppm) 7.87 (m, 2H), 7.50 (d, 1H, J 7.4), 7.29 (t, 1H, J 7.8), 5.76 (s, 1H), 4.38 (d, 1H, J 7.2), 3.84 (m, 1H), and 2.02 (m, 2H); ^{13}C NMR (63 MHz, D$_2$O) δ (ppm) 178.3, 147.9, 142.2, 139.9, 134.1, 129.8, 128.2, 123.1, 122.2, 73.4, 72.0, 69.9, and 38.6.

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(3-carboxylic)phenylcyclohex-5-en-1-carboxylic Acid (4h). Lactone **12h** (60 mg, 0.21 mmol), THF (1.9 mL), and aqueous lithium hydroxide (2.1 mL) were combined to produce a mixture. **4h** (50 mg, 83%) as a white amorphous solid. Retention time: 31 min. Mp 166−168 °C; $[\alpha]^{20}_{D}$ −80° (c 1.1, H$_2$O); ^{1}H NMR (250 MHz, D$_2$O) δ (ppm) 7.73 (m, 2H), 7.45 (d, 1H, J 7.5), 7.30 (t, 1H, J 7.7), 5.78 (s, 1H), 4.47 (d, 1H, J 7.2), 3.93 (m, 1H), 2.16 (d, 1H, J 13.3), and 2.07 (m, 1H); ^{13}C NMR (63 MHz, D$_2$O) δ (ppm) 178.5, 170.7, 143.3, 138.6, 132.5, 130.1, 129.4, 129.0, 128.4, 127.1, 73.5, 72.1, 69.9, and 38.6.

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(3,5-difluoro)phenylcyclohex-5-en-1-carboxylic Acid (4i). Lactone **12i** (75 mg, 0.28 mmol), THF (2.6 mL), and aqueous lithium hydroxide (1.4 mL) were combined to produce a mixture. **4i** (70 mg, 87%) as a white amorphous solid. Retention time: 27 min. Mp 114−119 °C; $[\alpha]^{20}_{D}$ −134° (c 1.1, CH$_3$OH); ^{1}H NMR (300 MHz, D$_2$O) δ (ppm) 6.85−6.71 (m, 3H), 5.79 (s, 1H), 4.38 (d, 1H, J 7.6), 3.90 (m, 1H), and 2.07 (m, 2H); ^{13}C NMR (75 MHz, D$_2$O) δ (ppm) 177.6, 162.7 (2×, J_{CF} 244 and 13), 142.4, 141.5 (J_{CF} 10), 127.2, 110.4 (J_{CF} 17), 110.3 (J_{CF} 17), 103.3 (J_{CF} 25), 73.0, 71.7, 69.6, and 38.3; ^{19}F NMR (282 MHz, D$_2$O) δ (ppm) −111.2 (t, 2F, J 8.7).

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(thiophen-3-yl)phenylcyclohex-5-en-1-carboxylic Acid (4j). Lactone **12j** (40 mg, 0.17 mmol), THF (1.5 mL), and aqueous lithium hydroxide (0.8 mL) were combined to produce a mixture. **4j** (40 mg, 93%) as a white amorphous solid. Retention time: 29 min. Mp 147−149 °C; $[\alpha]^{20}_{D}$ −74° (c 1.2, H$_2$O); ^{1}H NMR (300 MHz, D$_2$O) δ (ppm) 7.32 (m, 1H), 7.28−7.26 (m, 1H), 7.10 (m, 1H), 5.86 (s, 1H), 4.34 (d, 1H, J 6.3), 3.91−3.86 (m, 1H), and 2.02 (m, 2H); ^{13}C NMR (75 MHz, D$_2$O) δ (ppm) 182.4, 142.2, 140.2, 129.3, 129.2, 128.7, 125.7, 76.3, 74.2, 72.8, and 40.2.

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(pyridine-3-yl)cyclohex-5-en-1-carboxylic Acid (4k). Lactone **12k** (50 mg, 0.21 mmol), THF (1.9 mL), and aqueous lithium hydroxide (1.1 mL) were combined to produce a mixture. The aqueous extract was treated with Amberlite IR-120 until pH 5 and filtered. The resin was washed with 0.5 M ammonia until pH 8, filtered, and washed with water. The filtrate and the washings were lyophilized. **4k** (50 mg, 96%) as a white amorphous solid. Mp 196−198 °C; $[\alpha]^{20}_{D}$ −15° (c 1.1, H$_2$O); ^{1}H NMR (250 MHz, D$_2$O) δ (ppm) 8.70 (br s, 1H), 8.58 (br s, 1H), 8.50 (d, 1H, J 8.25), 7.93 (dd, 1H, J 7.75 and 6.0), 6.07 (s, 1H), 4.50 (d, 1H, J 6.75), 3.92 (m, 1H), and 2.07 (m, 2H); ^{13}C NMR (125 MHz, D$_2$O) δ (ppm) 183.6, 150.6, 149.9, 142.2, 139.1, 132.8, 130.3, 126.9, 76.9, 74.6, 73.0, and 41.5.

(1*R*,3*R*,4*R*)-1,3,4-Trihydroxy-5-(furan-3-yl)phenylcyclohex-5-en-1-carboxylic Acid (4l). Lactone **12l** (53 mg, 0.24 mmol), THF (2.2 mL), and aqueous lithium hydroxide (1.2 mL) were combined to produce a mixture. **4l** (56 mg, 98%) as a white amorphous solid. Retention time: 17 min. Mp 73−75 °C; $[\alpha]^{20}_{D}$ −59° (c 1.1, MeOH); ^{1}H NMR (300 MHz, CD$_3$OD) δ (ppm) 7.66 (s, 1H), 7.39 (br s, 1H), 6.54 (br s, 1H), 5.91 (s, 1H), 4.22 (d, 1H, J 6.9), 3.96 (m, 1H), and 2.18−2.02 (m, 2H); ^{13}C NMR (75 MHz, D$_2$O) δ (ppm) 177.8, 143.6, 141.2, 135.0, 123.3, 123.0, 108.7, 73.0, 71.7, 69.7, and 37.7.

Acknowledgment. Financial support from the Xunta de Galicia (Grant PGIDIT02RAG20901PR) and the Spanish Ministry of Education and Culture (Grant CTQ2004-04238) is gratefully acknowledged.

Supporting Information Available: IR, MS, and HRMS data for all compounds, elemental analysis results for **4**, ^{1}H NMR, ^{13}C NMR, and DEPT spectra of **4a**−**l**, and ^{19}F NMR spectra of **4b**−**e**,**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM0501836