# Parallel Solid-Phase Synthesis and Evaluation of Inhibitors of *Streptomyces coelicolor* Type II Dehydroquinase

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A series of 1-substituted and 4-substituted benzyl analogues of the known inhibitor (1*S*,3*R*,4*R*)-1,3,4-trihydroxy-5-cyclohexene-1-carboxylic acid has been synthesized and tested as inhibitors of *Streptomyces coelicolor* type II dehydroquinase. The solid-phase syntheses of 18 new analogues are reported. The most potent inhibitor, 2-nitrobenzyloxy analogue **5i**, has $K_i$ of 8 $\mu$M, more than 30 times lower than the $K_M$ of the substrate and approximately 4 times more potent than the original inhibitor. The binding modes of the synthesized analogues in the active site were studied by molecular docking with GOLD 2.0.

## Introduction

The shikimate pathway is the biosynthetic pathway to the aromatic amino acids phenylalanine, L-tryptophan, and L-tyrosine, as well as precursors to the folate coenzymes, alkaloids, and vitamins.[1] The pathway is present in bacteria, fungi, and plants and has been recently discovered in apicomplexan parasites.[2] Its absence from mammals has made this pathway an attractive target for the development of herbicides and antimicrobial agents. The successful herbicide Glyphosate acts by specifically inhibiting the sixth enzyme on the pathway.[3]

Dehydroquinase (3-dehydroquinate dehydratase) is the third enzyme on the shikimate pathway and is responsible for catalyzing the conversion of 3-dehydroquinic acid (**1**) to 3-dehydroshikimic acid (**2**) (Scheme 1). There are two forms of the enzyme, type I (e.g. from *Escherichia coli*)[4] and type II (e.g. from *Streptomyces coelicolor*).[5] The type I enzyme mechanism involves covalent imine intermediates between the enzyme and the substrate and proceeds with *syn* stereochemistry.[6] In contrast, the type II reaction proceeds through an enolate intermediate with overall *anti* stereochemistry.[7] These mechanistic and stereochemical distinctions have allowed us to design and synthesize compounds that are specific to either the type I[8] or type II[9] enzymes.

The enolate intermediate in the type II reaction is flattened relative to the 3-dehydroquinic acid (**1**). In addition, a negative charge is localized toward the enolate oxygen. Both of these features have been exploited in the design of first-generation inhibitors.[9] We have previously reported that analogue **3** (Scheme 2) showed a $K_i$ of 30 $\mu$M for *S. coelicolor* type II dehydroquinase. The crystal structure of *S. coelicolor* dehydroquinase with **3** bound in the active site has recently been solved.[10] This complex identifies a number of key interactions involved in inhibitor binding and sheds light on aspects of the catalytic mechanism of the enzyme. Also present in this structure was a molecule of glycerol, originated from the enzyme storage buffer, bound 3.7 Å away from the inhibitor **3**. This fact was used to design bifuntional inhibitors that straddle the two binding sites identified in the crystal structure of the enzyme.[11] The important observation that compounds with a double bond between C5−C6 bind in the manner predicted for transition state mimics encouraged us to design the next generation of inhibitors.

In this paper we describe attempts to make more potent inhibitors by incorporating binding interactions onto the core structure **3**. We describe the synthesis of 18 new analogues, **4a**−**i** and **5a**−**i** (Scheme 2), using solid-phase organic synthesis (SPOS). The inhibition studies and the molecular docking with these compounds against *S. coelicolor* type II dehydroquinase are also described.

**Synthesis of C-1 Substituted Analogues.** The strategy used for making the analogues **4a**−**i** involved the initial preparation of the resin **8** (Scheme 3). This was made from hydroxycarbolactone **7**, which was synthesized from benzoate **6** using our previously reported protocol.[12] Treatment of bromo-Wang resin[13] with the sodium alkoxide of lactone **7** afforded the lactone resin **8**. Although the reaction can be carried out using THF or DMF and at room temperature or 60 °C, the best results were obtained in DMF at 60 °C. The gel-phase FT-IR spectrum of the ether lactone resin **8** showed the lactone stretching band at 1797 $cm^{-1}$. Further evidence for the formation of **8** was obtained from examination of the gel-phase $^{13}C$ NMR spectrum. Distinctive signals for the TBS group were observed at 25.6 and −3.1 ppm. In addition, the signal for the methylene benzyl group moved from 34.0 ppm in bromo-Wang resin to 71.2 ppm in the lactone resin **8**.[14] Deprotection of the tertiary hydroxyl group in **8** was

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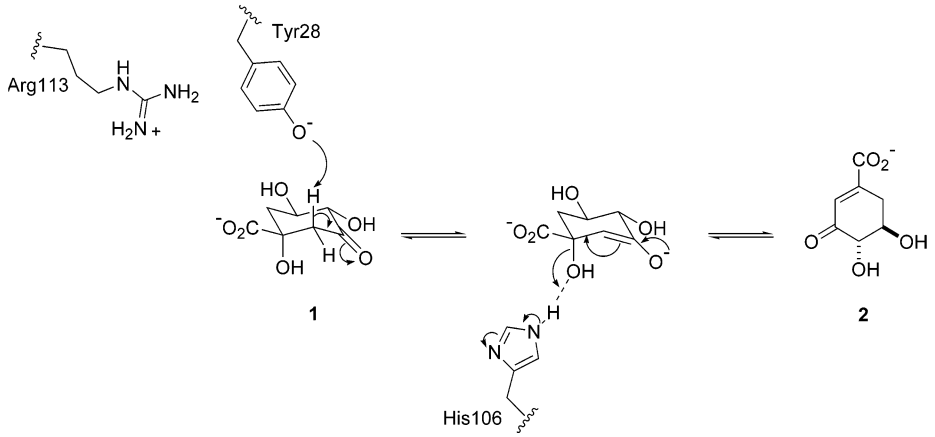
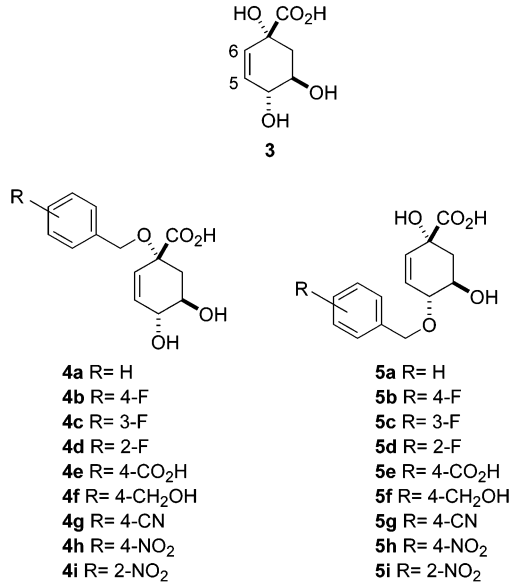
**Scheme 1.** Conversion of 3-Dehydroquinic Acid (1) to 3-Dehydroshikimic Acid (2) Catalyzed by Type II Dehydroquinase



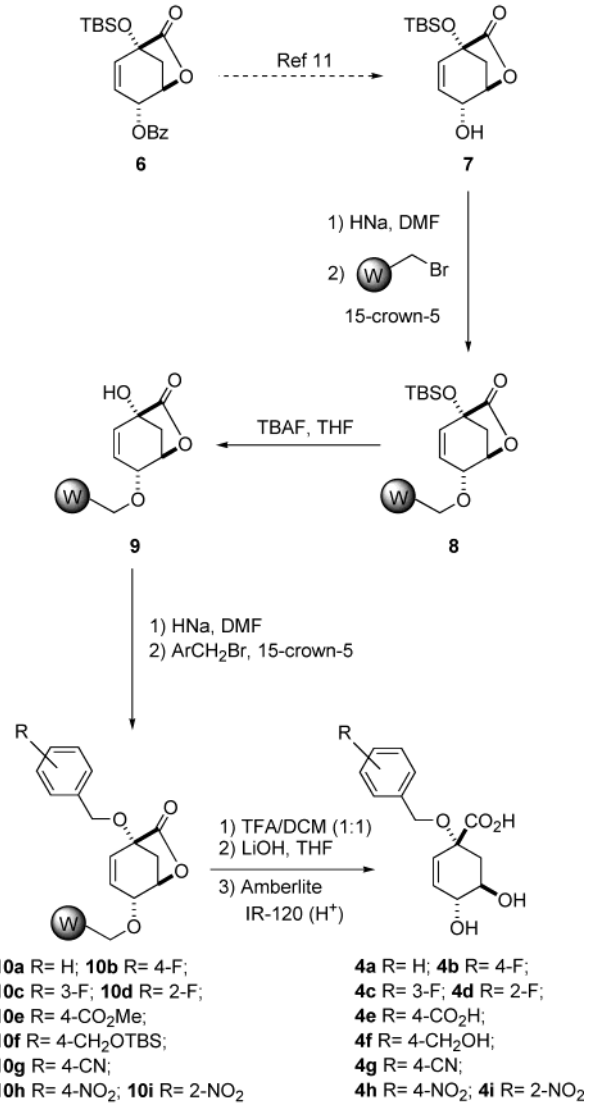

**Scheme 2.** *S. coelicolor* Type II Dehydroquinase Inhibitors



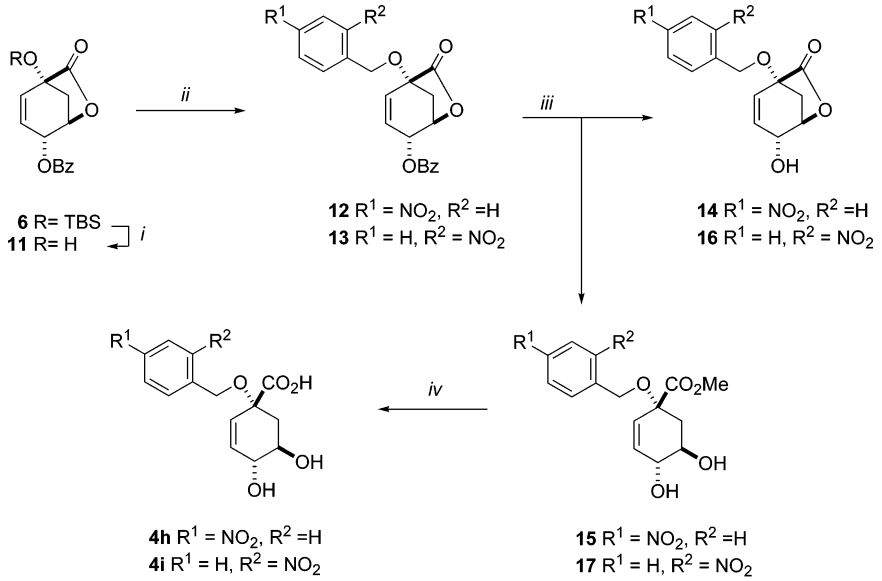

achieved by treatment of the lactone resin **8** with TBAF in THF at room temperature for 2 h. The gel-phase FT-IR spectrum of hydroxylactone resin **9** showed a strong band centered at 3414 $cm^{-1}$. The complete deprotection of the hydroxyl group was confirmed in the gel-phase $^{13}C$ NMR spectra of **9**.

Treatment of hydroxylactone resin **9** with sodium hydride in DMF at 0 °C followed by treatment with an excess of the corresponding benzyl bromide and heating between 40 and 80 °C gave the corresponding ethers **10a**−**i**.[15] This reaction was highly dependent on the nature of the benzyl bromide. Electron-donating groups reacted faster and required lower reaction temperatures (40 °C). Electron-withdrawing groups slowed the reaction and required higher temperatures (80 °C). The synthesis of the nitro derivatives was particularly problematical, and the reaction proceeded very slowly. The extent of conversion of each benzylation reaction was monitored by gel-phase FT-IR spectroscopy following the disappearance of the band at 3414 $cm^{-1}$ corresponding to the tertiary hydroxyl group of hydroxylactone **9**. The ether formation went to completion in all cases, except for the nitrobenzyl analogues. Treatment of the resins **10a**−**g** with 50% TFA/DCM at room temperature for 1 h afforded the corresponding lactones. Basic hydrolysis and washing the aqueous layer with diethyl ether to remove apolar impurities, followed by treatment with Amberlite IR-120 ($H^+$) ion-exchange resin and lyophilization, gave the desired acids **4a**−**g** in good yield and excellent purities.

**Scheme 3.** Parallel Solid-Phase Synthesis of C-1 Analogues

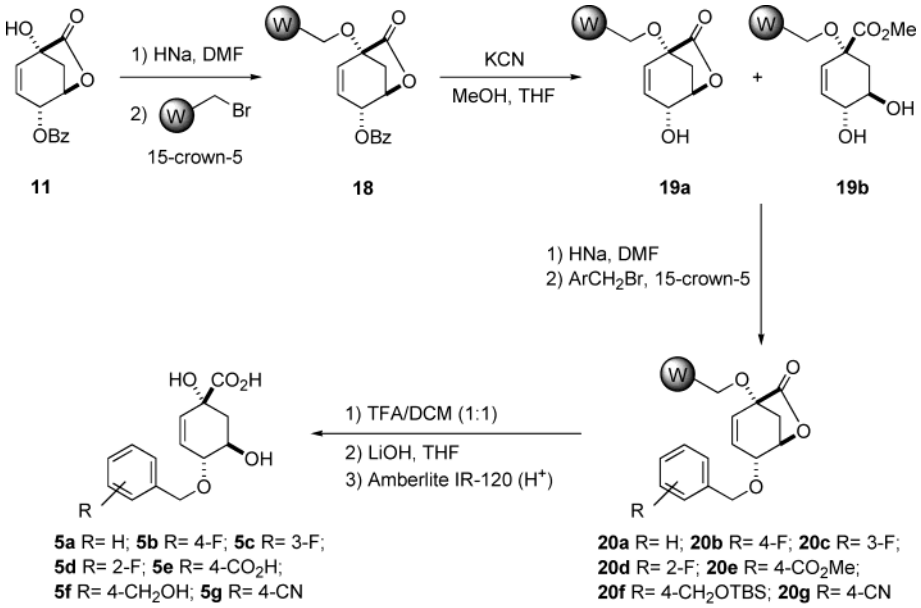


**Scheme 4**[a]




[a] Reagents and Conditions: (i) TBAF, THF, 0 °C (92%); (ii) (1) HNa, DMF, 0 °C; (2) nitrobenzyl bromide, 15-crown-5, 80 °C [**12** (41%); **13** (64%)]; (iii) KCN, MeOH, rt [**15** (60%) and **14** (traces); **16** (23%) and **17** (63%)]; (iv) (1) LiOH, THF, rt, (2) Amberlite IR-120 ($H^+$) [**4h** (96%), **4i** (78%)].

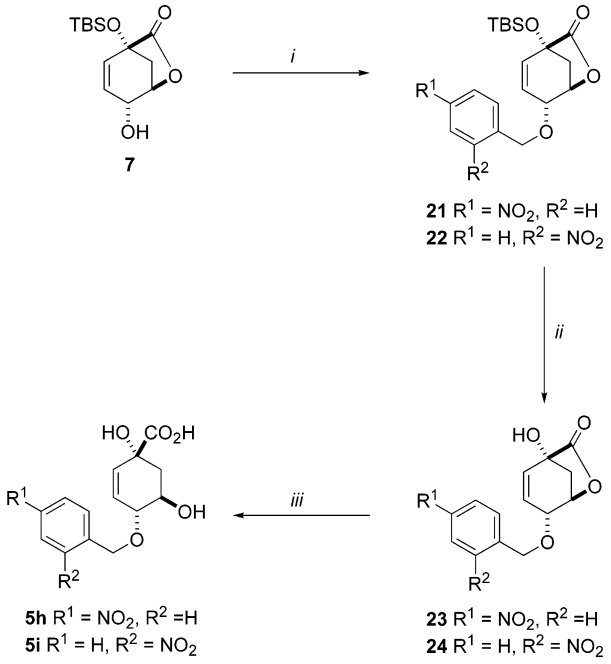
**Scheme 5.** Parallel Solid-Phase Synthesis of C-4 Analogues




Because of the slow reaction of **9** with nitrobenzyl bromide, the analogues **4h** and **4i** were eventually obtained as minor components in mixtures with unalkylated **3**. Consequently, we decided to prepare **4h** and **4i** by solution-phase synthesis. The four-step synthesis is outlined in Scheme 4. Treatment of the silyl ether derivative **6** with TBAF gave the desired tertiary alcohol **11** in excellent yield. Alkylation of the corresponding alkoxide of **11** with 4-nitrobenzyl bromide afforded the corresponding ether **12** in 41% yield (with 30% of recovered starting material). The best yields for the alkylation reaction were obtained when the reaction was performed in DMF at 80 °C for 48 h in the presence of a catalytic amount of 15-crown-5 ether. No significant difference was observed if sodium or potassium hydride was used. The benzoyl group was removed by treatment of the lactone **12** with potassium cyanide in methanol at room temperature to form the methyl ester **15** in 60% yield and traces of lactone **14**. Finally, conversion of methyl ester **15** to the desired acid **4h** was achieved by ester hydrolysis, followed by treatment with Amberlite IR-120 ($H^+$) ion-exchange resin and lyophilization. A similar strategy was used for the preparation of acid **4i** using 2-nitrobenzyl bromide.

**Synthesis of the 4-Substituted Analogues.** The 4-substituted benzyl analogues **5a**−**g** were prepared on solid-phase as outlined in Scheme 5. The strategy used for making analogues **5a**−**g** required the initial preparation of the resins **19a,b**. Alkylation of bromo-Wang resin with the corresponding sodium alkoxide of hydroxycarbolactone **11** in DMF at 80 °C afforded the desired benzyl ether resin **18**. The gel-phase FT-IR spectrum of ether resin **18** showed two new stretching bands centered at 1794 and 1718 $cm^{-1}$ corresponding

**Scheme 6**[a]




[a] Reagents and Conditions: (i) (1) HNa, DMF, 0 °C; (2) nitrobenzyl bromide, $Bu_4NI$, 15-crown-5, 80 °C [**21** (24%); **22** (54%)]; (ii) TBAF, THF, 0 °C [**23** (43%); **24** (71%)]; (iii) (1) LiOH, THF, rt, (2) Amberlite IR-120 (H) [**5h** (74%), **5i** (94%)].

to the new carbonyl groups. Examination of the gel-phase $^{13}C$ NMR spectrum showed distinctive signals at 73.6, 69.9, and 67.5 ppm.[14] Deprotection of the benzoyl group in resin **18** was achieved by treatment of **18** with potassium cyanide in methanol at room temperature for 2 h. This gave the resin **19** in two forms: as the carbolactone **19a** (minor) and as the methyl ester **19b** (major). The gel-phase FT-IR spectrum of hydroxy resins **19a,b** confirmed the disappearance of the benzoyl ester band at 1718 $cm^{-1}$. The spectra showed a new strong band at 1736 $cm^{-1}$ corresponding to the methyl ester and also the stretching band corresponding for the lactone at 1792 $cm^{-1}$. The alkylation of the resin **19a,b** was achieved by heated the corresponding sodium alkoxide of **19a,b** with the various benzyl bromides in DMF in the presence of a catalytic amount of 15-crown-5 ether. The extent of conversion was followed by monitoring the disappearance of the band at 3596 $cm^{-1}$ corresponding to the hydroxyl group in **19a,b** in the gel-phase FT-IR spectra. In all the cases the ether formation went to completion. Treatment of the resins **20a**−**g** with 50% TFA/DCM at room temperature for 1 h afforded the corresponding lactones. Finally, basic hydrolysis and washing the aqueous layer with diethyl ether, followed by treatment with Amberlite IR-120 ($H^+$) ion-exchange resin and lyophilization, afforded the desired acids **5a**−**g** in good yields and excellent purities.

It again proved problematical to make the nitrobenzyl analogues on solid-phase, so they were synthesied in solution as outlined in Scheme 6. Treatment of the corresponding sodium alkoxide of **7** with 4-nitrobenzyl bromide in DMF at 80 °C for 48 h in the presence of a catalytic amount of 15-crown-5 ether afforded the corresponding ether **21** in 24% yield, with recovery of 40% unreacted starting material. The silyl group was removed by treatment with TBAF to yield the corresponding tertiary alcohol **23**. Finally, treatment of lactone **23** with lithium hydroxide, followed by treatment with Amberlite IR-120 ($H^+$) ion-exchange resin and lyophilization, afforded the desired acid **5h**. Acid **5i** was prepared by a similar reaction sequence using 2-nitrobenzyl bromide.

**Table 1.** Inhibition Results for Assays with *S. coelicolor* Type II Dehydroquinase[a]

| compd | R | $K_i$ ($\mu$M) | compd | R | $K_i$ ($\mu$M) |
|---|---|---|---|---|---|
| **4a** | H | 380 ± 30 | **5a** | H | 200 ± 20 |
| **4b** | 4-F | 375 ± 30 | **5b** | 4-F | 70 ± 5 |
| **4c** | 3-F | 425 ± 40 | **5c** | 3-F | 140 ± 10 |
| **4d** | 2-F | 260 ± 20 | **5d** | 2-F | 130 ± 10 |
| **4e** | 4-$CO_2H$ | 170 ± 15 | **5e** | 4-$CO_2H$ | 100 ± 10 |
| **4f** | 4-$CH_2OH$ | 1330 ± 100 | **5f** | 4-$CH_2OH$ | >2000 |
| **4g** | 4-CN | 430 ± 40 | **5g** | 4-CN | 330 ± 30 |
| **4h** | 4-$NO_2$ | 980 ± 90 | **5h** | 4-$NO_2$ | 200 ± 20 |
| **4i** | 2-$NO_2$ | 45 ± 5 | **5i** | 2-$NO_2$ | 8 ± 2 |

[a] $K_M$ value of 250 $\mu$M was obtained at the assay conditions.

**Assay Results.** The 18 acids **4a**−**i** and **5a**−**i** were assayed in the presence of 3-dehydroquinic acid (**1**) for their inhibitory properties against *S. coelicolor* type II dehydroquinase. The inhibition data are summarized in Table 1. A 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 assays with **4e**, **5e**, **4g**, and **5g** were performed at 260 nm due to the strong UV absortion of these analogues at 234 nm. The $K_i$ values were obtained from Dixon plots ($1/v$ vs [I]).

All the compounds were shown to be reversible competitors of *S. coelicolor* type II dehydroquinase. The 4-substituted series was found to be generally more potent than the 1-substituted series. However, there was a general correlation across the two series. The three isomeric fluorobenzyl derivatives showed potency similar to or somewhat lower than the parent compound (**4a** and **5a**) in both series. The 2-nitro derivatives were the most potent compounds in each series. The 4-substituted analogue **5i** had a $K_i$ of 8 $\mu$M compared with 30 $\mu$M for the original inhibitor **3**, and considerably below the $K_M$ of 250 $\mu$M. The 4-carboxy benzyl derivatives **4e** and **5e** were both potent, the 4-cyano analogues **4g** and **5g** less so. The 4-hydroxymethyl compounds **4f** and **5f** were surprisingly poor inhibitors. The correlation between the two series broke down for the 4-nitrobenzyl derivatives, where the 1-substituted compound **4h** was considerably less potent than the 4-substituted analogue **5h**.

**Docking Studies.** To gain some insight into how the inhibitors were binding to the active site of *S. coelicolor* type II dehydroquinase, docking studies were carried out using GOLD 2.0.[16] The starting point for this study was the crystal structure of the enzyme with the anhydro inhibitor **3** bound in the active site.[10] This structure has the carboxyl group of **3** binding to the backbone amides of Ile107 and Ser108 and the C-1 hydroxyl binding to His106. There was an additional binding pocket close by that was occupied by a glycerol molecule (from the buffer). The molecule of **3**, the glycerol molecule, and all the water molecules except one (which is conserved in a series enzyme inhibitor complexes)[10] were removed from the structure. No energy minimization was performed on the enzyme. The structures of the inhibitors were prepared and energy-

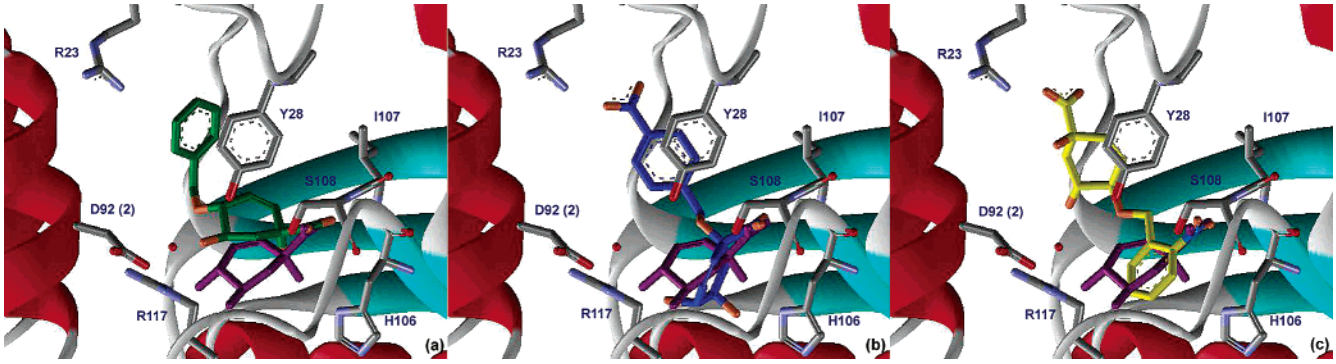



**Figure 1.** Comparison between position of **3** (purple) in the crystal structure of *S. coelicolor* type II dehydroquinase and the docking results of the highest score solution of (a) ligand **5a** (green), (b) ligand **4e** (blue), and (c) ligand **5i** (yellow).

minimized either using SYBYL6.5 and the Tripos force field or using Gaussian 98W[17] and AM1. All the inhibitors were docked as their carboxylate anions and 25 independent GOLD runs were performed for each ligand. The ChemScore scoring function was used.

The 4-substituted series **5a**−**i** (with the exception of **5i**) docked so that the anhydro ring of the inhibitor occupied approximately the same site as was occupied by **3** in the crystal structure of the enzyme inhibitor complex,[10] and the benzyl group occupied the pocket that had previously been occupied by the glycerol molecule (Figure 1a). The carboxyl and C-1 hydroxyl groups of the inhibitors occupied the same binding pocket as for **3**, although the orientation of the actual ring was twisted relative to the binding of **3**. The key binding interactions for the benzyl substituent appeared to be $\pi$ stacking against Tyr28 and electrostatic or hydrogen-bonding interactions with Arg23. The potency of the 4-carboxy and 4-nitro analogues **5e** and **5h** may be due to this latter interaction. The poor binding of the hydroxymethyl analogue **5f** may be because of limited space at the top of the binding pocket.

The 1-substituted series **4a**−**i** bound in a generally similar orientation to the 4-substituted series. The anhydro ring of the inhibitor occupied approximately the same site as was occupied by **3** in the crystal structure of the enzyme−inhibitor complex, and the benzyl group occupied the pocket that had previously been occupied by the glycerol molecule (Figure 1b). However, the different position of the benzyl substituent on the anhydro ring led to some differences in the binding relative to the 4-substituted series. These are most clearly seen in a different orientation of the anhydro ring, caused by the need to put the benzyl group into the glycerol pocket. The carboxyl group still bound into the carboxylate binding pocket, but in some analogues the anhydro ring was conformationally flipped so that the C-5 hydroxyl group can bind to His106. The benzyl substitutent occupied a similar position to that found for the 4-substituted series, with the same interactions with Tyr28 and Arg23. The latter interaction may again be responsible for the relative potency of the 4-carboxybenzyl analogue **4e**.

The one anomalous result from the docking study was the binding predicted for the most potent inhibitor **5i**, the 4-substituted 2-nitrobenzyl analogue. This suggested that the relative positions of the two rings was reversed, so that the benzyl group occupied the binding site occupied by **3**, with the nitro group binding into the carboxylate binding site (Figure 1c). The anhydro ring docked into the glycerol pocket, with the carboxylate binding to Arg23. This result is surprising and may be an artifact of the way the active site is prepared for the docking (if more of the original water molecules are retained, docking similar to that for the other 4-substitued analogues was observed).

These docking studies have proved useful in giving some clues as to the possible binding orientations of the analogues and have highlighted some possible interactions that can be targeted in the next generation of inhibitors. However, they need to be supported with structural studies of enzyme−inhibitor complexes, and these are underway.

## Conclusions

Solid-phase organic synthesis and solution-phase synthesis have been used to make a series of 1-benzylated and 4-benzylated analogues of the known inhibitor **3**. The 4-substituted 2-nitrobenzyl analogue **5i** was found to have a $K_i$ of 8 $\mu$M, making it one of the most potent known inhibitor against any type II dehydroquinase. Docking studies have identified two binding pockets likely to be occupied by the inhibitor and provide some rationale for the relative potencies of the 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 1 D, 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 alternately with water, 10% NaOH, water, 10% HCl, and finally water before use. Purity of the carboxylic acids was analyzed by HPLC and NMR. HPLC was performed on a preparative (300 mm × 16 mm) Bio-Rad Aminex Ion exclusion HPX-87H organic acids column. The eluant used for these columns was 75 mM aqueous formic acid, at a flow rate of 0.6 mL min$^{-1}$.

**Dehydroquinase Assay.** *S. coelicolor* type II dehydroquinase was purified as described previously,[5] as a concentrated solution (1.5 mg mL$^{-1}$) in potassium phosphate buffer (50 mM, pH 7.0); DTT (1 mM) was filter-sterilized through a 0.2 $\mu$m filter and stored at 4 °C under which conditions it was stable for at least 9 months. When required for assays, aliquots

of the enzyme stocks were diluted into water and buffer and stored on ice.

Dehydroquinase was assayed in the forward direction by monitoring the increase in absorbance at 234 nm in the UV spectrum due to the absorbance of the enone−carboxylate chromophore of 3-dehydroshikimic acid (**2**) ($\epsilon$/$M^{-1}$ $cm^{-1}$ 12 000). Standard assay conditions for type II dehydroquinase were pH 7.0 at 25 °C in Tris/HCl (50 mM). Each assay was initiated by addition of the enzyme. 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**). In the case of acids **4e**, **5e**, **4g**, and **5g**, assays were performed at 260 nm.

**Docking.** The receptor and ligands were used as MOL2 files. Each ligand was docked using GOLD 2.0 in 25 independent genetic algorithm (GA) runs, and for each of these a maximum number of 100 000 GA operations was 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.

**Preparation of Resin 8.** To a stirred solution of the alcohol **7**[12] (1.4 g, 5.18 mmol) in dry DMF (20 mL) at 0 °C under inert atmosphere was added sodium hydride (222 mg, 5.54 mmol, ca. 60% in mineral oil). After 30 min at this temperature the resultant suspension was added *via* cannula to a preswollen PS-brominated Wang resin[13] (1 g, ∼1.6 mmol/g, ∼1.6 mmol) in dry DMF (17 mL) at 0 °C and under inert atmosphere. Then, 15-crown-5 ether (30 $\mu$L, 0.26 mmol) was added and the resultant suspension was shook at 0 °C for 30 min and at room temperature for 24 h. The resin was thoroughly washed with DMF, DMF−water (3:1), THF, and dry DCM and dried under high vacuum to afford pale yellow beads of **8** (1.02 g): gel-phase FTIR ($cm^{-1}$) 1797 and 1611; gel-phase $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 128.5, 118.7, 114.7, 73.7, 71.2, 69.9, 64.8, 40.4, 37.7, 25.6, and −3.1.

**Preparation of Resin 9.** To preswollen resin **8** (1 g, ∼1 mmol) in dry THF (16 mL) at 0 °C and under inert atmosphere was added a solution of tetrabuthylammonium fluoride in THF (1.4 mL, ca. 1 M in THF). The resultant suspension was shook for 2 h at room temperature. The resin was thoroughly washed with THF, THF−5% HCl (3:1), THF, and dry DCM to afford after drying in vacuo pale yellow beads of resin **9** (∼0.9 g): gel-phase FTIR ($cm^{-1}$) 3414, 1789, and 1609; gel-phase $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 136.4, 129.5, 121.5, 115.3, 74.6, 71.1, 53.5, and 36.9.

**General Procedure for the Preparation of Resins 10a−g and 20a−g.** To preswollen resin in dry DMF at 0 °C and under inert atmosphere was added sodium hydride (6 equiv, ca. 60% in mineral oil). The resultant suspension was shook for 1 h at room temperature, and then the corresponding bromide (10 equiv) and 15-crown-5 ether (0.3 equiv) were added. The resin was gently stirred and heated between 40 and 80 °C for 24−48 h. The resin was thoroughly washed with THF, THF−10% HCl (3:1), THF, and dry DCM to afford after drying in vacuo resins **10a−i** and **20a−g**.

**General Cleavage Procedure.** The resin was treated with (1:1) TFA−DCM (1 mL per 100 mg of resin) at room temperature for 1 h. The resin was filtered and washed with dry DCM. The filtrate was evaporated and dried in vacuo. The obtained residue was redissolved in THF and treated with 5 equiv of 0.5 M aqueous lithium hydroxide. The mixture was stirred for 30 min and then it was diluted with water and washed with diethyl ether (3×). The aqueous extract was treated with Amberlite IR-120 (H+) until pH 6. The resin was filtered and washed with water. The filtrate was lyophilized to afford a colorless oil or a foam unless specified.

**(1*R*,3*R*,4*R*)-1-Benzyloxy-3,4-dihydroxycyclohex-5-en-1-carboxylic acid (4a):** 85% overall; retention time 25 min; $[\alpha]_D^{25}$ +15° (*c* 0.7 in $H_2O$); $^1H$ NMR (250 MHz, $D_2O$) $\delta$ (ppm) 7.31 (m, 5H), 5.93 (d, 1H, *J* 10.1), 5.82 (dd, 1H, *J* 10.1 and 1.8), 4.41 (s, 2H), 4.00 (dd, 1H, *J* 8.3 and 1.8), 3.77 (td, 1H, *J* 11.9, 8.3, and 3.5), 2.14 (dd, 1H, *J* 13.6 and 3.5), and 1.87 (dd, 1H, *J* 13.6 and 11.9); $^{13}C$ NMR (100 MHz, $D_2O$) $\delta$ (ppm) 178.1, 137.9, 134.2, 128.8, 128.8, 128.4, 127.3, 80.8, 72.6, 69.5, 67.7, and 37.9; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3434, 1714, and 1578; MS (CI) *m*/*z* (%) 247 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{15}O_4$ ($MH^+ - H_2O$) 247.0970, found 247.0965.

**(1*R*,3*R*,4*R*)-1-(4′-Fluorobenzyloxy)-3,4-dihydroxycyclohex-5-en-1-carboxylic acid (4b):** 67% overall; retention time 26 min; $[\alpha]_D^{25}$ +9° (*c* 1.0 in $H_2O$); $^{19}F$ NMR (282 MHz, $D_2O$) $\delta$ (ppm) −112.6 (tt, 1F, *J* 9.1 and 5.2); $^1H$ NMR (250 MHz, $D_2O$) $\delta$ (ppm) 7.32 (dd, 2H, *J* 7.7 and 5.7), 7.04 (t, 2H, *J* 8.7), 5.91 (m, 2H), 4.40 (s, 2H), 4.03 (dd, 1H, *J* 8.2 and 1.2), 3.78 (ddd, 1H, *J* 11.6, 8.2, and 3.5), 2.15 (dd, 1H, *J* 13.6 and 3.5), and 1.90 (dd, 1H, *J* 13.6 and 11.6); $^{13}C$ NMR (63 MHz, $D_2O$) $\delta$ (ppm) 177.8, 162.7 (*J* 242), 134.8, 133.8, 131.1 (*J* 8), 127.0, 115.6 (*J* 21), 80.3, 72.7, 69.6, 67.2, and 38.0; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3420, 1716, and 1605; MS (CI) *m*/*z* (%) 265 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{14}O_4F$ ($MH^+ - H_2O$) 265.0876, found 263.0880.

**(1*R*,3*R*,4*R*)-1-(3′-Fluorobenzyloxy)-3,4-dihydroxycyclohex-5-en-1-carboxylic acid (4c):** 63% overall; retention time 29 min; $[\alpha]_D^{25}$ +11° (*c* 0.6 in $H_2O$); $^{19}F$ NMR (282 MHz, $D_2O$) $\delta$ (ppm) −111.8 (dt, 1F, *J* 9.6 and 5.6); $^1H$ NMR (250 MHz, $D_2O$) $\delta$ (ppm) 7.61 (m, 1H), 7.43−7.26 (m, 3H), 6.23 (d, 1H, *J* 10.1), 6.14 (dd, 1H, *J* 10.1 and 1.8), 4.72 (s, 2H), 4.31 (dt, 1H, *J* 8.2 and 1.8), 4.08 (ddd, 1H, *J* 12.2, 8.2, and 3.7), 2.44 (ddd, 1H, *J* 13.6, 3.0, and 1.1), and 2.19 (dd, 1H, *J* 13.6 and 12.2); $^{13}C$ NMR (63 MHz, $D_2O$) $\delta$ (ppm) 175.2, 162.9 (*J* 242), 140.6 (*J* 7), 134.6, 130.6 (*J* 8), 127.2, 124.5 (*J* 3), 115.4 (*J* 21), 115.1 (*J* 21), 80.0, 72.7, 69.6, 67.1, and 38.2; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3400, 1716, and 1592; MS (CI) *m*/*z* (%) 265 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{14}O_4F$ ($MH^+ - H_2O$) 265.0876, found 265.0870.

**(1*R*,3*R*,4*R*)-1-(2′-Fluorobenzyloxy)-3,4-dihydroxycyclohex-5-en-1-carboxylic acid (4d):** 70% overall; retention time 28 min; $[\alpha]_D^{25}$ −5° (*c* 0.7 in $H_2O$); $^{19}F$ NMR (282 MHz, $D_2O$) $\delta$ (ppm) −117.0 (dt, 1F, *J* 10.5 and 6.3); $^1H$ NMR (250 MHz, $D_2O$) $\delta$ (ppm) 7.41−7.29 (m, 2H), 7.15−7.02 (m, 2H), 5.94 (d, 1H, *J* 10.1), 5.86 (dd, 1H, *J* 10.1 and 1.7), 4.50 (s, 2H), 4.02 (dt, 1H, *J* 8.2 and 1.7), 3.78 (ddd, 1H, *J* 12.1, 8.2, and 3.6), 2.18 (ddd, 1H, *J* 13.7, 3.6, and 1.4), and 1.90 (dd, 1H, *J* 13.7 and 12.1); $^{13}C$ NMR (63 MHz, $D_2O$) $\delta$ (ppm) 177.8, 161.2 (*J* 244), 135.0, 131.8 (*J* 4), 130.9 (*J* 8), 127.0, 124.6 (*J* 18), 124.7, 115.7 (*J* 21), 80.3, 72.7, 69.6, 61.6 (*J* 4), and 37.8 ($CH_2$); $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3420, 1717, and 1589; MS (CI) *m*/*z* (%) 265 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{14}O_4F$ ($MH^+ - H_2O$) 265.0876, found 265.0876.

**(1*R*,3*R*,4*R*)-3,4-Dihydroxy-1-(4′-carboxy)benzyloxycyclohex-5-en-1-carboxylic acid (4e):** 65% overall; retention time 27.5 min; mp 161−162 °C; $[\alpha]_D^{25}$ +16° (*c* 1.3 in $CH_3OH$); $^1H$ NMR (250 MHz, $CD_3OD$) $\delta$ (ppm) 7.94 (d, 2H, *J* 8.2), 7.45 (d, 2H, *J* 8.2), 6.01 (d, 1H, *J* 10.1), 5.87 (dd, 1H, *J* 10.1 and 1.9), 4.61 (d, 1H, *J* 11.8), 4.54 (d, 1H, *J* 11.8), 3.99−3.82 (m, 2H), 2.26 (dd, 1H, *J* 13.2 and 3.4), and 1.96 (dd, 1H, *J* 13.2 and 11.5); $^{13}C$ NMR (63 MHz, $CD_3OD$) $\delta$ (ppm) 177.0, 170.0, 145.6, 135.7, 130.6, 128.5, 128.2, 80.7, 74.1, 70.9, 67.5, and 30.8; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3444 and 1697; MS (CI) *m*/*z* (%) 291 ($MH^+$ $^-$ $H_2O$); HRMS calcd for $C_{15}H_{15}O_6$ ($MH^+ - H_2O$) 291.0869, found 291.0873.

**(1*R*,3*R*,4*R*)-3,4-Dihydroxy-1-(4′-hydroxymethyl)benzyloxycyclohex-5-en-1-carboxylic acid (4f):** 75% overall; retention time 21 min; mp 143−144 °C; $[\alpha]^{25}$ +21° (*c* 0.8 in $CH_3OH$); $^1H$ NMR (250 MHz, $CD_3OD$) $\delta$ (ppm) 7.30 (d, 2H, *J* 8.3), 7.24 (d, 2H, *J* 8.3), 5.97 (d, 1H, *J* 10.1), 5.85 (dd, 1H, *J* 10.1 and 1.9), 4.52 (s, 2H), 4.47 (d, 1H, *J* 11.0), 4.42 (d, 1H, *J* 11.0), 3.93 (dt, 1H, *J* 7.9 and 1.9), 3.83 (ddd, 1H, *J* 11.6, 7.9, and 3.5), 2.22 (m, 1H), and 1.90 (dd, 1H, *J* 13.3 and 11.6); $^{13}C$ NMR (63 MHz, $CD_3OD$) $\delta$ (ppm) 176.7, 141.9, 139.0, 135.9, 129.1, 127.9, 127.8, 80.4, 74.1, 70.8, 68.0, 65.0, and 39.6; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3372 and 1699; MS (CI) *m*/*z* (%) 259 ($MH^+ - 2H_2O$); HRMS calcd for $C_{15}H_{15}O_4$ ($MH^+ - 2H_2O$) 259.0970, found 259.0967.

**(1*R*,3*R*,4*R*)-3,4-Dihydroxy-1-(4′-cyano)benzyloxycyclohex-5-en-1-carboxylic acid (4g):** 70% overall; retention time 33 min; mp 81−82 °C; $[\alpha]_D^{25}$ +18° (*c* 0.6 in $CH_3OH$); $^1H$ NMR (250 MHz, $CD_3OD$) $\delta$ (ppm) 7.66 (d, 2H, *J* 8.3), 7.55 (d, 2H, *J* 8.3), 6.01 (d, 1H, *J* 10.1), 5.87 (dd, 1H, *J* 10.1 and 2.0), 4.64 (d, 1H, *J* 12.3), 4.56 (d, 1H, *J* 12.3), 3.98 (dt, 1H, *J* 7.8, 2.0, and 1.8), 3.86 (ddd, 1H, *J* 11.5, 7.8, and 3.6), 2.26 (ddd, 1H, *J* 13.3, 3.6, and 2.2), and 1.98 (dd, 1H, *J* 13.3 and 11.5); $^{13}C$ NMR (63 MHz, $CD_3OD$) $\delta$ (ppm) 177.2, 146.4, 135.7, 133.1, 129.3, 128.3, 119.8, 111.9, 80.8, 74.1, 70.9, 67.1, and 39.7; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3410, 2232, and 1716; MS (CI) *m*/*z* (%) 272 ($MH^+ - H_2O$); HRMS calcd for $C_{15}H_{14}NO_4$ ($MH^+ - H_2O$) 272.0923, found 272.0930.

**(1*R*,3*R*,4*R*)-4-Benzoyloxy-1-hydroxycyclohex-5-en-1,3-carbolactone (11).** To a stirred solution of the silyl ether **6** (2.16 g, 5.78 mmol), under argon and at 0 °C, in 80 mL of a dry THF, was added tetrabutylammonium fluoride (6.4 mL, 6.36 mmol, ca. 1.0 M in THF). After stirring for 30 min, dilute HCl was added and the organic layer was extracted with DCM (3×). The combined organic extracts were dried (anhydrous $Na_2SO_4$) and concentrated under reduced pressure. The crude reaction was purified by flash cromatography eluting with 75% diethyl ether−hexanes and recrystallized from hexane to yield the alcohol **11** as white needles (1.38 g, 92%): $[\alpha]_D^{25}$ −103° (*c* 0.6 in $CHCl_3$); mp 104−105 °C (hexane); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ (ppm) 8.03 (dd, 2H, *J* 8.5 and 1.4), 7.60 (m, 1H), 7.46 (t, 1H, *J* 7.5), 6.30 (d, 1H, *J* 9.7), 5.88 (ddd, 1H, *J* 9.7, 3.3, and 1.1), 5.54 (t, 1H, *J* 3.0), 4.90 (m, 1H), 3.79 (br s, 1H), 2.55 (ddd, 1H, *J* 11.7, 5.2, and 1.7), and 2.49 (d, 1H, *J* 11.7); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 177.1, 165.2, 138.6, 133.7, 129.8, 128.9, 128.6, 124.2, 74.3, 73.3, 66.1, and 37.2; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3478, 1775, and 1722; MS (CI) *m*/*z* (%) 261 $(MH)^+$; HRMS calcd for $C_{14}H_{13}O_5$ ($MH^+$) 261.0763, found 261.0755. Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.60; H, 4.65. Found: C, 64.60; H, 4.65.

**(1*R*,3*R*,4*R*)-4-Benzoyloxy-1-(4′-nitrobenzyloxy)cyclohex-5-en-1,3-carbolactone (12).** To a stirred solution of the alcohol **11** (93 mg, 0.36 mmol) in dry DMF (1.6 mL) at 0 °C under inert atmosphere was added sodium hydride (17 mg, 0.43 mmol, ca. 60% in mineral oil). After 30 min at this temperature 4-nitrobenzyl bromide (156 mg, 0.72 mmol), tetrabutylammonium iodide (27 mg, 0.07 mmol), and 15-crown-5 ether (10 $\mu$L, 0.04 mmol) were added. The resultant blue suspension was heated at 80 °C for 24 h. The suspension was diluted successively with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). All the combined organic layers were dried (anhydrous $Na_2SO_4$), filtered, and evaporated. The crude residue was purified by flash chromatography eluting with 70% DCM−hexanes to afford 58 mg (41%) of ether **12** as an amorphous pale yellow solid and also 28 mg (30%) of starting material was recovered: mp 135−136 °C (diethyl ether); $[\alpha]_D^{25}$ −254° (*c* 0.9 in $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ (ppm) 8.23 (dt, 2H, *J* 8.8 and 2.1), 8.04 (dt, 2H, *J* 7.0, and 1.5), 7.60 (m, 3H), 7.46 (m, 2H), 6.41 (dd, 1H, *J* 9.8 and 2.0), 5.98 (ddd, 1H, *J* 9.8, 3.4, and 2.1), 5.57 (t, 1H, *J* 3.0), 4.93 (m, 1H), 4.84 (d, 1H, *J* 12.6), 4.79 (d, 1H, *J* 12.6), 2.71 (ddd, 1H, *J* 10.9, 6.0, and 2.0), and 2.40 (d, 1H, *J* 10.9); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 173.1, 165.1, 147.6, 144.5, 136.2, 133.8, 129.8, 128.9, 128.6, 127.8, 125.0, 123.7, 78.9, 73.5, 66.4, 66.3, and 33.9; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 1801, 1722, and 1604; MS (CI) *m*/*z* (%) 396 ($MH^+$); HRMS calcd for $C_{21}H_{18}NO_7$ ($MH^+$) 396.1083, found 396.1066.

**Methyl (1*R*,3*R*,4*R*)-3,4-Dihydroxy-1-(4′-nitrobenzyloxy)-cyclohex-5-en-1-carboxylate (15).** To a stirred suspension of the benzoate **12** (62 mg, 0.16 mmol) in dry methanol (1.5 mL) was added potassium cyanide (12 mg, 0.18 mmol). The resultant red solution was stirred at room temperature for 1 h. DCM was added and then water. The organic layer was separated and the aqueous layer 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 40% ethyl acetate−hexanes to yield diol **15** (31 mg, 60%) as a pale yellow oil: $[\alpha]_D^{25}$ +5° (*c* 0.9 in $CH_3OH$); $^1H$ NMR (250 MHz, $CD_3OD$) $\delta$ (ppm) 8.24 (br d, 2H, *J* 8.9), 7.69 (br d, 2H, *J* 8.9), 6.00 (s, 2H), 4.73 (d, 1H, *J* 12.6), 4.67 (d, 1H, *J* 12.6), 4.39 (br s, 1H), 4.26 (br s, 1H), 4.03 (m, 1H), 3.91 (m, 1H), 3.77 (s, 3H), 2.30 (ddd, 1H, *J* 13.5, 3.6, and 0.9), and 1.98 (dd, 1H, *J* 13.5 and 11.7); $^{13}C$ NMR (62.5 MHz, $CD_3OD$) $\delta$ (ppm) 172.1, 146.9, 146.3, 136.3, 127.7, 124.4, 122.9, 78.8, 72.8, 69.1, 65.4, 51.5, and 38.0; $\upsilon_{max}$ (NaCl)/$cm^{-1}$ 3390, 1740, and 1606; MS (CI) *m*/*z* (%) 306 ($MH^+ - H_2O$); HRMS calcd for $C_{15}H_{16}NO_6$ ($MH^+ - H_2O$) 306.0978, found 306.0978.

**(1*R*,3*R*,4*R*)-3,4-Dihydroxy-1-(4′-nitrobenzyloxy)cyclohex-5-en-1-carboxylic Acid (4h).** A solution of the methyl ester **15** (25 mg, 0.08 mmol) in 0.5 mL of THF and 0.4 mL of 0.5 M aqueous lithium hydroxide was stirred at room temperature for 1 h. The resultant solution was diluted with water and treated with Amberlite IR-120 ($H^+$) until pH 6. The resin was filtered and washed with water. The filtrate was concentrated to afford acid **4h** (23 mg, 96%) as a pale yellow oil: retention time 40 min; $[\alpha]_D^{25}$ +13° (*c* 2.2 in $CH_3OH$); $^1H$ NMR (250 MHz, $CD_3OD$) $\delta$ (ppm) 8.38 (d, 2H, *J* 8.7), 7.82 (d, 2H, *J* 8.7), 6.23 (d, 1H, *J* 10.0), 6.09 (d, 1H, *J* 10.0 and 1.8), 4.90 (d, 1H, *J* 12.6), 4.82 (d, 1H, *J* 12.6), 4.20 (br d, 1H, *J* 7.8), 4.07 (m, 1H), 2.48 (br d, 1H, *J* 12.8), and 2.20 (dd, 1H, *J* 12.8 and 11.8); $^{13}C$ NMR (63 MHz, $CD_3OD$) $\delta$ (ppm) 177.5, 148.8, 148.6, 136.1, 129.5, 128.5, 124.5, 81.2, 74.3, 71.2, 67.2, and 40.0; $\upsilon_{max}$ (KBr)/$cm^{-1}$ 3419, 1718, and 1604; MS (CI) *m*/*z* (%) 292 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{14}NO_6$ ($MH^+ - H_2O$) 292.0821, found 292.0821.

**(1*R*,3*R*,4*R*)-4-Benzoyloxy-1-(2′-nitrobenzyloxy)cyclohex-5-en-1,3-carbolactone (13).** To a stirred solution of the alcohol **11** (200 mg, 0.77 mmol) in dry DMF (7 mL) at 0 °C under inert atmosphere was added sodium hydride (37 mg, 0.92 mmol, ca. 60% in mineral oil). After 30 min at this temperature 2-nitrobenzyl bromide (216 mg, 1.00 mmol), tetrabutylammonium iodide (28 mg, 0.08 mmol), and 15-crown-5 ether (20 $\mu$L, 0.08 mmol) were added. The resultant blue suspension was heated at 80 °C for 24 h. The suspension was diluted successively with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). All the combined organic layers were dried (anhydrous $Na_2SO_4$), filtered, and evaporated. The crude residue was purified by flash chromatography eluting with 70% DCM−hexanes to afford 196 mg (64%) of ether **13** as amorphous beige solid and also 24 mg of starting material (12%) was recovered: $[\alpha]_D^{25}$ −290° (*c* 1.5 in $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ (ppm) 8.05 (m, 4H), 7.70 (t, 1H, *J* 7.6), 7.61 (t, 1H, *J* 7.4), 7.47 (t, 3H, *J* 7.5), 6.43 (dd, 1H, *J* 9.8 and 1.5), 5.98 (ddd, 1H, *J* 9.8, 3.3, and 1.3), 5.57 (t, 1H, *J* 3.1), 5.17 (d, 1H, *J* 14.3), 5.01 (d, 1H, *J* 14.3), 4.94 (m, 1H), 2.74 (ddd, 1H, *J* 10.9, 6.1, and 1.9), and 2.50 (d, 1H, *J* 10.9); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 173.0, 165.1, 146.7, 136.3, 134.0, 133.7, 129.8, 128.9, 128.9, 128.6, 128.4, 125.3, 124.7, 78.7, 73.6, 66.2, 64.3, and 33.8; $\upsilon_{max}$ (NaCl)/$cm^{-1}$ 1793 and 1718; MS (CI) *m*/*z* (%) 396 ($MH^+$); HRMS calcd for $C_{21}H_{18}NO_7$ ($MH^+$) 396.1083, found 396.1083.

**(1*R*,3*R*,4*R*)-4-Hydroxy-1-(2′-nitrobenzyloxy)cyclohex-5-en-1,3-carbolactone (16) and Methyl (1*R*,3*R*,4*R*)-3,4-Dihydroxy-1-(2′-nitrobenzyloxy)cyclohex-5-en-1-carboxylate (17).** To a stirred suspention of the benzoate **13** (127 mg, 0.32 mmol) in dry methanol (3 mL) was added potassium cyanide (24 mg, 0.37 mmol). The resultant solution was stirred at room temperature for 1 h. DCM was added and then water. The organic layer was separated and the aqueous layer 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 diethyl ether−ethyl acetate (90:10) to yield carbolactone **16** (24 mg, 26%) and diol **17** (65 mg, 63%).

Data for carbolactone **16**: $[\alpha]_D^{25}$ −175° (*c* 1.4 in $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ (ppm) 8.10 (dd, 1H, *J* 8.2 and 1.3), 7.96 (dd, 1H, *J* 7.9 and 1.0), 7.68 (m, 1H), 7.47 (m, 1H), 6.25 (dd, 1H, *J* 9.8 and 1.6), 5.87 (ddd, 1H, *J* 9.8, 3.3, and 1.2), 5.11 (d, 1H, *J* 14.4), 4.95 (d, 1H, *J* 14.4), 4.74 (m, 1H), 4.33 (t, 1H, *J* 3.1), 2.61 (ddd, 1H, *J* 10.9, 6.1, and 2.1), and 2.40 (d, 1H, *J* 10.9); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 173.8, 146.7, 134.4,

134.0, 133.8, 128.9, 128.4, 128.3, 124.8, 79.1, 76.2, 65.1, 64.2, and 32.8; $\nu_{max}$ (NaCl)/cm$^{-1}$ 3459 and 1790; MS (CI) *m*/*z* (%) 292 ($MH^+$); HRMS calcd for $C_{14}H_{14}NO_6$ ($MH^+$) 292.0821, found 292.0827.

Data for diol **17**: $[\alpha]_D^{25}$ +43° (*c* 1.5 in $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) (ppm) $\delta$ 7.97 (dd, 1H, *J* 8.2 and 1.0), 7.79 (dd, 1H, *J* 7.8 and 1.0), 7.60 (dt, 1H, *J* 7.6 and 1.0), 7.38 (dt, 1H, *J* 7.8 and 1.0), 5.95 (s, 2H), 4.84 (d, 1H, *J* 14.5), 4.78 (d, 1H, *J* 14.5), 4.08 (d, 1H, *J* 8.0), 3.93 (m, 1H), 3.72 (s, 3H), 2.33 (dd, 1H, *J* 13.6 and 3.1), and 1.98 (dd, 1H, *J* 13.6 and 12.1); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 172.4, 147.1, 135.8, 134.2, 133.7, 129.3, 128.1, 125.1, 124.4, 78.8, 73.2, 69.8, 63.8, 52.7, and 38.0; $\nu_{max}$ (NaCl)/cm$^{-1}$ 3390 and 1739; MS (CI) *m*/*z* (%) 292 ($MH^+ - HOCH_3$); HRMS calcd for $C_{14}H_{14}NO_6$ ($MH^+ - HOCH_3$) 292.0821, found 292.0823.

**(1*R*,3*R*,4*R*)-3,4-Dihydroxy-1-(2′-nitrobenzyloxy)cyclohex-5-en-1-carboxylic Acid (4i).** A solution of the methyl ester **17** (65 mg, 0.20 mmol) in 2 mL of THF and 1 mL of 0.5 M aqueous lithium hydroxide was stirred at room temperature for 1 h. The resultant solution was diluted with water and treated with Amberlite IR-120 ($H^+$) until pH 6. The resin was filtered and washed with water. The filtrate was concentrated to afford acid **4i** (48 mg, 78%) as a beige oil: retention time 35 min; $[\alpha]_D^{25}$ −19° (*c* 0.7 in $CH_3OH$); $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ (ppm) 7.96 (dd, 1H, *J* 8.2 and 1.1), 7.87 (br d, 1H, *J* 7.9), 7.63 (m, 1H), 7.42 (m, 1H), 5.97 (d, 1H, *J* 10.1), 5.86 (d, 1H, *J* 10.1), 4.84 (s, 2H), 3.94 (d, 1H, *J* 7.8), 3.85 (m, 1H), 2.26 (br d, 1H, *J* 13.6), and 1.96 (dd, 1H, *J* 13.6 and 12.0); $^{13}$C NMR (63 MHz, $CD_3OH$) $\delta$ (ppm) 178.4, 148.6, 136.7, 135.1, 134.5, 131.5, 128.9, 125.2, 73.6, 73.2, 71.2, 64.4, and 39.7; $\nu_{max}$ (KBr)/cm$^{-1}$ 3398, 1707, and 1578; MS (CI) *m*/*z* (%) 292 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{14}NO_6$ ($MH^+ - H_2O$) 292.0821, found 292.0820.

**Preparation of Resin 18.** To a stirred solution of the alcohol **11** (1.43 g, 5.48 mmol) in dry DMF (25 mL) at 0 °C under inert atmosphere was added sodium hydride (264 mg, 6.60 mmol, ca. 60% in mineral oil). After 30 min at this temperature the resultant suspension was added *via* cannula to a preswollen PS-brominated Wang resin (1.4 g, ∼1.6 mmol/g, ∼2.24 mmol) in dry DMF (16 mL) at 0 °C and under inert atmosphere. Then, 15-crown-5 ether (60 $\mu$L, 0.32 mmol) was added and the resultant suspension was shook at 0 °C for 30 min and at 80 °C for 48 h. The resin was thoroughly washed with DMF, DMF−water (3:1), THF, and dry DCM and dried under high vacuum to afford brown beads of **11** (1.4 g): gel-phase FTIR (cm$^{-1}$) 1794, 1718, and 1611; gel-phase $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 137.0, 133.6, 129.5, 114.6, 73.6, 70.0, 67.5, 40.4, and 34.0.

**Preparation of Resin 19.** To preswollen resin **18** (1.1 g, ∼1.3 mmol) in dry THF (6 mL) was added a solution of potassium cyanide (136 mg, 2.09 mmol) in methanol (2 mL). The resultant suspension was bubbled through with argon for 2 h at room temperature. The resin was thoroughly washed with THF, methanol, THF, and dry DCM to afford after drying in vacuo pale brown beads of resin **19** (∼1 g): gel-phase FTIR (cm$^{-1}$) 3392, 1792, 1732, and 1604; gel-phase $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 129.6, 114.6, 70.2, 67.4, 53.4, and 40.4.

**(1*R*,3*R*,4*R*)-4-Benzyloxy-1,3-dihydroxycyclohex-5-en-1-carboxylic acid (5a)**: 75% overall; retention time 27 min; $[\alpha]_D^{25}$ −128° (*c* 3.4 in $H_2O$); $^1$H NMR (250 MHz, $D_2O$) $\delta$ (ppm) 7.15−7.03 (m, 5H), 5.65 (dd, 1H, *J* 9.8 and 1.6), 5.41 (d, 1H, *J* 9.8), 4.44 (d, 1H, *J* 13.8), 4.39 (d, 1H, *J* 13.8), 3.77−3.60 (m, 2H), and 1.74 (d, 2H, *J* 6.2); $^{13}$C NMR (63 MHz, $CD_3OD$) $\delta$ (ppm) 177.8, 139.0, 131.3, 130.6, 128.9, 129.0, 128.6, 81.0, 75.0, 72.7, 69.1, and 40.8; $\nu_{max}$ (KBr)/cm$^{-1}$ 3420 and 1706; MS (+FAB) *m*/*z* (%) 247 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{15}O_4$ ($MH^+ - H_2O$) 247.0970, found 247.0964.

**(1*R*,3*R*,4*R*)-4-(4′-Fluorobenzyloxy)-1,3-dihydroxycyclohex-5-en-1-carboxylic acid (5b)**: 72% overall; retention time 28 min; $[\alpha]_D^{25}$ −133° (*c* 0.9 in $H_2O$); $^{19}$F NMR (282 MHz, $D_2O$) $\delta$ (ppm) −112.5 (tt, 1F, *J* 9.2 and 5.2); $^1$H NMR (250 MHz, $D_2O$) $\delta$ (ppm) 7.35 (t, 2H, *J* 5.8), 7.04 (t, 2H, *J* 8.3), 5.87 (d, 1H, *J* 9.7), 5.65 (d, 1H, *J* 9.7), 4.61 (s, 2H), 3.92 (m, 2H), and 1.98 (d, 2H, *J* 6.8); $^{13}$C NMR (63 MHz, $D_2O$) $\delta$ (ppm) 179.0, 162.8 (*J* 242), 133.5, 131.0 (*J* 8), 130.9, 128.9, 115.7 (*J* 21), 80.0, 74.2, 71.3, 67.8, and 39.7; $\nu_{max}$ (Nujol)/cm$^{-1}$ 3391, 3333, and 1713; MS (CI) *m*/*z* (%) 265 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{14}O_4F$ ($MH^+ - H_2O$) 265.0876, found 265.0875.

**(1*R*,3*R*,4*R*)-4-(3′-Fluorobenzyloxy)-1,3-dihydroxycyclohex-5-en-1-carboxylic acid (5c):** 75% overall; retention time 31 min; $[\alpha]_D^{25}$ −127° (*c* 0.9 in $H_2O$); $^{19}$F NMR (282 MHz, $D_2O$) $\delta$ (ppm) −111.6 (dt, 1F, *J* 9.5 and 5.6); $^1$H NMR (250 MHz, $D_2O$) $\delta$ (ppm) 7.21 (m, 1H), 7.04 (m, 2H), 6.92 (m, 1H), 5.79 (d, 1H, *J* 10.0), 5.61 (d, 1H, *J* 10.0), 4.55 (s, 2H), 3.86 (m, 2H), and 1.94 (d, 2H, *J* 6.0); $^{13}$C NMR (63 MHz, $D_2O$) $\delta$ (ppm) 178.1, 162.9 (*J* 245), 140.3 (*J* 7), 131.1, 130.6 (*J* 8), 128.5, 124.4 (*J* 3), 115.3 (*J* 22), 115.2 (*J* 21), 80.2, 73.9, 71.2, 67.7, and 39.5; $\nu_{max}$ (NaCl)/cm$^{-1}$ 3410 and 1726; MS (CI) *m*/*z* (%) 283 ($MH^+$); HRMS calcd for $C_{14}H_{16}O_5F$ ($MH^+$) 283.0982, found 283.0978.

**(1*R*,3*R*,4*R*)-4-(2′-Fluorobenzyloxy)-1,3-dihydroxycyclohex-2-en-1-carboxylic acid (5d):** 70% overall; retention time 29 min; $[\alpha]_D^{25}$ −134° (*c* 3.0 in $H_2O$); $^{19}$F NMR (282 MHz, $D_2O$) $\delta$ (ppm) −116.9 (dt, 1F, *J* 10.5 and 6.4); $^1$H NMR (250 MHz, $D_2O$) $\delta$ (ppm) 7.26 (t, 1H, *J* 7.2), 7.13 (m, 1H), 6.98 (t, 1H, *J* 7.0), 6.90 (t, 1H, *J* 8.9), 5.70 (d, 1H, *J* 9.9), 5.55 (d, 1H, *J* 9.9), 4.55 (s, 2H), 3.83 (m, 2H), and 1.92 (m, 2H); $^{13}$C NMR (63 MHz, $D_2O$) $\delta$ (ppm) 178.2, 161.2 (*J* 245), 131.5 (*J* 4), 130.9, 130.8 (*J* 10), 128.7, 124.7 (*J* 3), 124.5 (*J* 15), 115.7 (*J* 21), 80.4, 73.9, 67.7, 65.9 (*J* 3), and 39.5; $\nu_{max}$ (Nujol)/cm$^{-1}$ 3430 and 1718; MS (CI) *m*/*z* (%) 283 ($MH^+$); HRMS calcd for $C_{14}H_{16}O_5F$ ($MH^+$) 283.0982, found 283.0970.

**(1*R*,3*R*,4*R*)-4-(4′-Carboxybenzyloxy)-1,3-dihydroxycyclohex-5-en-1-carboxylic acid (5e):** 68% overall; retention time 32 min; mp 187−188 °C; $[\alpha]_D^{25}$ −152° (*c* 1.1 in $CH_3OH$); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ (ppm) 7.98 (d, 2H, *J* 7.8), 7.50 (d, 2H, *J* 7.8), 5.90 (dd, 1H, *J* 1.8 and 9.9), 5.71 (d, 1H, *J* 9.9), 4.80 (s, 2H), 4.04 (m, 1H), 3.92 (d, 1H, *J* 7.5), and 2.10 (m, 2H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ (ppm) 177.7, 168.9, 144.6, 130.0, 130.0, 129.8, 127.5, 80.5, 73.6, 71.0, 68.2, and 39.9; $\nu_{max}$ (KBr)/cm$^{-1}$ 3423 and 1699; MS (CI) *m*/*z* (%) 291 ($MH^+ - H_2O$); HRMS calcd for $C_{15}H_{14}O_6$ ($MH^+ - H_2O$) 291.0869, found 291.0880.

**(1*R*,3*R*,4*R*)-1-Hydroxy-4-(4′-hydroxymethyl)benzyloxycyclohex-5-en-1-carboxylic acid (5f):** 77% overall; retention time 21 min; $[\alpha]_D^{25}$ −136° (*c* 1.3 in $CH_3OH$); $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ (ppm) 7.42 (d, 2H, *J* 8.1), 7.36 (d, 2H, *J* 8.1), 5.90 (dd, 1H, *J* 10.0 and 1.7), 5.72 (d, 1H, *J* 10.0), 4.75 (s, 2H), 4.62 (s, 2H), 4.06 (m, 1H), 3.93 (d, 1H, *J* 7.4), and 2.11 (m, 2H); $^{13}$C NMR (63 MHz, $CD_3OD$) $\delta$ (ppm) 178.6, 142.1, 138.9, 131.2, 130.7, 129.1, 128.0, 81.0, 74.6, 72.6, 69.2, 64.9, and 40.0; $\nu_{max}$ (NaCl)/cm$^{-1}$ 3364 and 1730; MS (CI) *m*/*z* (%) 277 ($MH^+ - H_2O$); HRMS calcd for $C_{15}H_{17}O_5$ ($MH^+ - H_2O$) 277.1076, found 277.1083.

**(1*R*,3*R*,4*R*)-1,3-Dihydroxy-4-(4′-cyanobenzyloxy)cyclohex-5-en-1-carboxylic acid (5g):** 70% overall; retention time 37 min; mp 137−138 °C; $[\alpha]_D^{25}$ −157° (*c* 1.0 in $CH_3OH$); $^1$H NMR (300 MHz, $D_2O$) $\delta$ (ppm) 7.40 (d, 2H, *J* 7.8), 7.28 (d, 2H, *J* 7.8), 5.72 (d, 1H, *J* 9.9), 5.57 (d, 1H, *J* 9.9), 4.55 (s, 2H), 3.84 (m, 2H), and 1.92 (d, 2H, *J* 7.2); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ (ppm) 178.3, 143.6, 132.6, 130.4, 129.0, 128.5, 119.6, 110.4, 80.4, 73.9, 70.7, 67.8, and 39.6; $\nu_{max}$ (KBr)/cm$^{-1}$ 3398, 2231, and 1720; MS (CI) *m*/*z* (%) 272 ($MH^+ - H_2O$); HRMS calcd for $C_{15}H_{14}O_4N$ ($MH^+ - H_2O$) 272.0923, found 272.0923.

**(1*R*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-(4′-nitrobenzyloxy)cyclohex-5-en-1,3-carbolactone (21).** To a stirred solution of the alcohol **7** (164 mg, 0.61 mmol) in dry DMF (6 mL) at 0 °C under inert atmosphere was added sodium hydride (29 mg, 0.73 mmol, ca. 60% in mineral oil). After 30 min at this temperature 4-nitrobenzyl bromide (171 mg, 0.79 mmol), tetrabutylammonium iodide (23 mg, 0.06 mmol), and 15-crown-5 ether (10 $\mu$L, 0.08 mmol) were added. The resultant blue suspension was heated at 80 °C for 48 h. The suspension was diluted successively with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). All the combined organic layers were dried (anhydrous $Na_2SO_4$), filtered, and evaporated. The crude residue was purified by flash chromatography eluting with 70% DCM−hexanes to afford 60 mg

(24%) of ether **21** as amorphous pale yellow solid: $[\alpha]_D^{25}$ −172° (*c* 2.0 in $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ (ppm) 8.21 (d, 2H, *J* 8.8), 7.50 (d, 2H, *J* 8.8), 6.15 (ddd, 1H, *J* 9.8, 1.7, and 1.0), 5.78 (ddd, 1H, *J* 9.8, 3.2, and 1.1), 4.77 (s, 2H), 4.73 (m, 1H), 3.98 (t, 1H, *J* 3.2), 2.42 (ddd, 1H, *J* 10.6, 5.2, and 1.8), 2.37 (d, 1H, *J* 10.6), 0.90 (s, 9H), 0.17 (s, 3H), and 0.14 (s, 3H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 175.3, 147.5, 144.9, 138.9, 127.7, 124.2, 123.7, 75.0, 73.4, 72.4, 70.9, 37.7, 25.5, 17.9, and −3.1; $\upsilon_{max}$ (NaCl)/cm$^{-1}$ 1793; MS (CI) *m*/*z* (%) 406 ($MH^+$); HRMS calcd for $C_{20}H_{28}O_6NSi$ ($MH^+$) 406.1686, found 406.1676.

**(1*R*,3*R*,4*R*)-1-Hydroxy-4-(4′-nitrobenzyloxy)cyclohex-5-en-1,3-carbolactone (23).** To a stirred solution of the silyl ether **21** (95 mg, 0.23 mmol), under argon and at 0 °C, in 2 mL of dry THF, was added tetrabutylammonium fluoride (0.25 mL, 0.25 mmol, ca. 1.0 M in THF). After stirring for 30 min, dilute HCl was added and the organic layer was extracted with DCM (3×). The combined organic extracts were dried (anhydrous $Na_2SO_4$) and concentrated under reduced pressure. The crude reaction product was purified by flash cromatography eluting with diethyl ether to afford alcohol **23** as a pale yellow oil (29 mg, 43%): $[\alpha]_D^{25}$ −265.5° (*c* 1.2, in $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ (ppm) 8.22 (d, 2H, *J* 8.7), 7.51 (d, 2H, *J* 8.7), 6.17 (d, 1H, *J* 9.8), 5.82 (ddd, 1H, *J* 9.8, 3.3, and 1.0), 4.81 (m, 1H), 4.78 (s, 2H), 4.02 (t, 1H, *J* 3.3), 3.35 (br s, 1H), and 2.44 (m, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 177.2, 147.6, 144.8, 137.4, 127.7, 125.1, 123.8, 74.5, 73.4, 72.2, 71.0, and 36.9; $\upsilon_{max}$ (NaCl)/cm$^{-1}$ 3405 and 1784; MS (CI) *m*/*z* (%) 292 ($MH^+$); HRMS calcd for $C_{14}H_{14}O_6N$ ($MH^+$) 292.0821, found 292.0826.

**(1*R*,3*R*,4*R*)-1,3-Dihydroxy-4-(4′-nitrobenzyloxy)cyclohex-5-en-1-carboxylic Acid (5h).** A solution of the carbolactone **23** (28 mg, 0.10 mmol) in 1 mL of THF and 0.5 mL of 0.5 M aqueous lithium hydroxide was stirred at room temperature for 1 h. The resultant solution was diluted with water and treated with Amberlite IR-120 until pH 6. The resin was filtered and washed with water. The filtrate was concentrated to afford acid **5h** (23 mg, 74%) as a pale yellow amorphous solid: retention time 48 min; $[\alpha]_D^{25}$ −121° (*c* 1.1, in $CH_3OH$); $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ (ppm) 8.20 (d, 2H, *J* 8.8), 7.65 (d, 2H, *J* 8.8), 5.93 (dd, 1H, *J* 10.0 and 1.8), 5.73 (d, 1H, *J* 10.0), 4.84 (s, 2H), 4.04 (m, 1H), 3.93 (dt, 1H, *J* 7.9 and 1.8), and 2.07 (m, 2H); $^{13}$C NMR (63 MHz, $CD_3OD$) $\delta$ (ppm) 176.8, 147.6, 147.1, 130.4, 129.3, 128.1, 123.4, 81.1, 73.5, 70.4, 68.2, and 40.2; $\upsilon_{max}$ (KBr)/cm$^{-1}$ 3528 and 1596; MS (CI) *m*/*z* (%) 310 ($MH^+$); HRMS calcd for $C_{14}H_{16}NO_7$ ($MH^+$) 310.0928, found 310.0928.

**(1*R*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-(2′-nitrobenzyloxy)cyclohex-5-en-1,3-carbolactone (22).** To a stirred solution of the alcohol **7** (138 mg, 0.51 mmol) in dry DMF (4 mL) at 0 °C under inert atmosphere was added sodium hydride (27 mg, 0.66 mmol, ca. 60% in mineral oil). After 30 min at this temperature 2-nitrobenzyl bromide (165 mg, 0.77 mmol), tetrabutylammonium fluoride (28 mg, 0.08 mmol), and 15-crown-5 ether (10 $\mu$L, 0.08 mmol) were added. The resultant blue suspension was heated at 80 °C for 24 h. The suspension was diluted successively with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). All the combined organic layers were dried (anhydrous $Na_2SO_4$), filtered, and evaporated. The crude residue was purified by flash chromatography eluting with 25% diethyl ether−hexanes to afford 111 mg (54%) of ether **22** as amorphous beige solid: $[\alpha]_D^{25}$ −205° (*c* 1.2 in $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ (ppm) 8.06 (dd, 1H, *J* 8.1 and 1.0), 7.67 (m, 2H), 7.48 (dt, 1H, *J* 8.2 and 1.8), 6.15 (dd, 1H, *J* 9.8 and 1.7), 5.81 (ddd, 1H, *J* 9.8, 3.3, and 1.9), 5.08 (d, 1H, *J* 13.9), 5.00 (d, 1H, *J* 13.9), 4.78 (m, 1H), 4.02 (t, 1H, *J* 3.1), 2.43 (ddd, 1H, *J* 10.8, 5.8, and 1.9), 2.33 (d, 1H, *J* 10.8), 0.91 (s, 9H), 0.18 (s, 3H), and 0.14 (s, 3H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 175.4, 147.4, 138.7, 133.6, 129.0, 128.6, 124.7, 124.3, 75.0, 73.2, 72.5, 69.0, 37.7, 25.5, 17.9, and −3.2; $\upsilon_{max}$ (NaCl)/cm$^{-1}$ 1798; MS (CI) *m*/*z* (%) 406 ($MH^+$); HRMS calcd for $C_{20}H_{28}O_6NSi$ ($MH^+$) 406.1686, found 406.1703.

**(1*R*,3*R*,4*R*)-1-Hydroxy-4-(2′-nitrobenzyloxy)cyclohex-5-en-1,3-carbolactone (24).** To a stirred solution of the silyl ether **22** (165 mg, 0.41 mmol), under argon and at 0 °C, in 4 mL of a dry THF, was added tetrabutylammonium fluoride (0.45 mL, 0.45 mmol, ca. 1.0 M in THF). After stirring for 30 min, dilute HCl was added and the organic layer was extracted with DCM (3×). The combined organic extracts were dried (anhydrous $Na_2SO_4$) and concentrated under reduced pressure. The crude reaction was purified by flash cromatography eluting with 75% diethyl ether−hexanes to yield the alcohol **24** as beige oil (85 mg, 71%): $[\alpha]_D^{25}$ −269° (*c* 0.9 in $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ (ppm) 8.04 (dd, 1H, *J* 8.1 and 1.2), 7.74−7.61 (m, 2H), 7.46 (dt, 1H, *J* 8.1 and 1.8), 6.16 (ddd, 1H, *J* 9.8, 1.5, and 0.7), 5.84 (ddd, 1H, *J* 9.8, 3.4, and 1.1), 5.08 (d, 1H, *J* 14.0), 5.00 (d, 1H, *J* 14.0), 4.85 (m, 1H), 4.05 (dt, 1H, *J* 3.4 and 0.7), 3.81 (br s, 1H), 2.46 (ddd, 1H, *J* 11.0, 5.4, and 1.5) and 2.39 (d, 1H, *J* 11.0); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ (ppm) 177.5, 147.3, 137.0, 133.7, 133.6, 128.9, 128.6, 125.1, 124.8, 74.3, 73.4, 72.4, 69.0, and 36.8; $\upsilon_{max}$ (NaCl)/cm$^{-1}$ 3432 and 1790; MS (CI) *m*/*z* (%) 292 ($MH^+$); HRMS calcd for $C_{14}H_{14}O_6N$ ($MH^+$) 292.0821, found 292.0824.

**(1*R*,3*R*,4*R*)-1,3-Dihydroxy-4-(2′-nitrobenzyloxy)cyclohex-5-en-1-carboxylic Acid (5i).** A solution of the carbolactone **24** (23 mg, 0.08 mmol) in 1 mL of THF and 0.4 mL of 0.5 M aqueous lithium hydroxide was stirred at room temperature for 1 h. The resultant solution was diluted with water and treated with Amberlite IR-120 ($H^+$) until pH 6. The resin was filtered and washed with water. The filtrate was concentrated to afford acid **5h** (23 mg, 94%) as a beige amorphous solid: retention time 46 min; $[\alpha]_D^{25}$ −59° (*c* 1.0, in $CH_3OH$); $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 8.01 (dd, 1H, *J* 8.1 and 1.2), 7.89 (br d, 1H, *J* 8.4), 7.68 (dt, 1H, *J* 7.6 and 1.2), 7.49 (m, 1H), 5.89 (d, 1H, *J* 9.7), 5.72 (d, 1H, *J* 9.7), 5.09 (br s, 2H), 4.03 (m, 1H), 3.93 (d, 1H, *J* 7.5), and 2.05 (m, 2H); $^{13}$C NMR (63 MHz, $CD_3OD$) $\delta$ 176.7, 148.1, 135.0, 133.5, 130.4, 129.6, 129.3, 128.4, 124.4, 81.3, 73.6, 68.7, 68.4, and 40.1; $\upsilon_{max}$ (NaCl)/cm$^{-1}$ 3397, 1716, and 1609; MS (CI) *m*/*z* (%) 292 ($MH^+ - H_2O$); HRMS calcd for $C_{14}H_{14}O_6N$ ($MH^+ - H_2O$): 292.0821, found 292.0819.

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**Supporting Information Available:** Copies of $^1$H NMR and $^{13}$C NMR spectra of compounds **4a**−**i** and **5a**−**i**, $^{19}$F NMR spectra of compounds **4b**−**d** and **5b**−**d**, and gel-phase $^{13}$C NMR spectra of **8**, **9**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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