

Stereoselective Photochemical 1.3-Dioxolane Addition to 5-Alkoxymethyl-2(5H)-furanone: Synthesis of **Bis-tetrahydrofuranyl Ligand for HIV Protease Inhibitor UIC-94017 (TMC-114)**

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A convenient synthesis of (3R, 3aS, 6aR)-3-hydroxyhexahydrofuro[2, 3-b] furan, a high-affinity nonpeptidal ligand for HIV protease inhibitor UIC-94017, is described. This inhibitor is undergoing advanced clinical trials. The synthesis utilizes a novel stereoselective photochemical 1,3-dioxolane addition to 5(S)-benzyloxymethyl-2(5H)-furanone as the key step. The requisite furanone derivative was prepared in high enantiomeric excess by an immobilized lipase-catalyzed selective acylation of (\pm) -1-(benzyloxy)-3-buten-2-ol and a ring-closing olefin metathesis with Grubbs' catalyst. Optically active bis-THF was converted to protease inhibitor 2 (UIC-94017).

Introduction

The therapeutic inhibition of the proteolytic enzyme HIV protease continues to be an effective target for AIDS chemotherapy. Combination therapy consisting of HIV protease inhibitors and reverse transcriptase inhibitors has emerged as a major treatment regimen for AIDS.¹ These therapies have significantly improved the course of HIV management and halted the progression of AIDS. However, the majority of protease inhibitors contain substantial peptide-like features and as a result possess the traditional problems of peptide-based drugs. Furthermore, rapid emergence of drug resistance to these protease inhibitors can make these therapies ineffective.² In view of these problems, the current emphasis in antiprotease therapies has been to design and synthesize nonpeptidal protease inhibitors that are potent against mutant strains resistant to the currently approved protease inhibitors.³ Such strategies may substantially delay the emergence of clinical resistance as well as alleviate the problems of "peptide-based" drugs.

We recently reported a series of very potent nonpeptidyl HIV protease inhibitors incorporating structurebased novel high-affinity P_2 -ligands and (R)-(hydroxyethylamino)sulfonamide isosteres.⁴ Of particular interest, inhibitors 1 and 2 (Figure 1) incorporating a structure-based designed bis-tetrahydrofuranyl ligand as the



FIGURE 1. Structures of inhibitors 1 and 2, bis-THF ligand, and isostere.

P2-ligand, provided remarkably improved enzyme inhibitory and antiviral potencies (1, $K_i = 15 \pm 1$ pM, n = 4, and $ID_{50} = 1.4 \pm 0.25 \text{ nM}$, n = 5; **2**, $K_i = 16 \pm 1 \text{ pM}$, n =2, and $ID_{50} = 3 \pm 0.01$ nM, n = 3).⁵ The significance of P2-bis-THF ligand over 3(S)-THF ligand in withstanding critical drug-resistance has now been well documented.5a,6 Inhibitor 2 (UIC-94017, now renamed TMC-114) is currently undergoing advanced clinical trials.⁷ Our previous route to optically active bis-tetrahydrofuran involved a

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racemic synthesis followed by an enzymatic resolution at the final stage.⁸ While this synthesis is potentially applicable for large-scale synthesis of optically active bis-THF, the synthetic route is not easily amenable to introduction of other substituents, particularly at the C2, C4, or C5 positions. To avoid late-stage resolution and to further explore the biological properties of inhibitors incorporating other substituents, we sought to develop an alternative route to bis-tetrahydrofuran in optically active form. Herein we report a convenient synthesis of (3R,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furan (3) in high enantiomeric excess utilizing a stereoselective photochemical 1,3-dioxolane addition as the key step. The requisite 5(S)-benzyloxymethyl-2(5H)-furanone was prepared conveniently by an immobilized lipase-catalyzed selective acylation of (\pm) -1-(benzyloxy)-3-buten-2-ol and a ring-closing olefin metathesis with Grubbs' catalyst. Optically active bis-THF so obtained was converted to

Results and Discussion

protease inhibitor 2 (UIC-94017).

Our synthetic strategy focused on a stereoselective photochemical conjugate addition of 1,3-dioxolane to a protected 5(S)-hydroxymethyl-2(5H)-furanone derivative. Fraser-Reid⁹ and Paquette¹⁰ previously reported photochemical addition of alcohols and utilized this reaction in synthesis. A survey of the literature reveals that the related photochemical addition of 1,3-dioxolane to α,β unsaturated ketones proceeded with good to excellent isolated yields.¹¹ Diastereoselective photochemical addition of 1,3-dioxolane to the chiral 4-methyleneoxazolidin-5-one has also been reported to proceed with good diastereoselectivities.¹² Diastereoselective photochemical addition of 1,3-dioxolane to butenolides, however, has very little precedence. There exists a single example where 1,3-dioxolane addition to 5(S)-hydroxymethyl-2(5H)-furanone was carried out in the absence of benzophenone providing anti-photoadduct in 54% yield.^{13,14} We therefore planned to investigate photochemical conjugate addition of 1,3-dioxolane to a range of protected 5(S)-hydroxymethyl-2(5H)-furanone derivatives.

The corresponding substrates for photochemical addition can be prepared by protection of 5(S)-hydroxymethyl-2(5H)-furanone which is commercially available, although quite expensive.¹⁵ Other syntheses of furanone derivatives have been previously reported.¹⁶ We planned to prepare 5(S)-benzyloxymethyl-2(5H)-furanone by using

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- (14) Diastereoselectivity of addition has not been reported, presumably the product was obtained as a single diastereomer.
- (15) (S)-Hydroxymethyl-2(5H)-furanone is available commercially for a price of \$108.70 for 1 g.

SCHEME 1. Optically Active Synthesis of Dihydrofuranone



a biocatalytic route that presents reasonable potential for scale-up. The biocatalytic resolution process would provide access to the other enantiomer as well. For synthesis and ready access to optically active furanone derivatives, we investigated a new synthetic route that involves an enzymatic resolution of racemic starting material followed by ring-closing olefin metathesis of the derived acrylate ester. Various protected furanone derivatives for photochemical studies have been prepared by a second route that utilized a cis-olefination and lactonization of readily available optically active isopropylidene-D-glyceraldehyde. Scheme 1 depicts our synthesis of optically active 5(S)-bezyloxymethyl-2(5H)-furanone using an efficient biocatalytic process. Racemic allylic alcohol 6 was prepared in multigram quantities by treatment of commercial benzyloxyacetaldehyde (5) with vinylmagnesium bromide in THF at 0 °C for 1 h. Enzymatic acylation of the racemic alcohol 6 with immobilized lipase PS-30 $(25 \text{ wt } \%)^{17}$ in the presence of isopropenyl acetate in dimethoxyethane at 23 °C for 48 h offered the best result. This condition afforded the optically active desired 6S-enantiomer (49% yield, 99% ee) and the acylated alcohol 7 (49% yield), which were separated by silica gel chromatography.¹⁸ When the enzymatic resolution of racemic alcohol was carried out on a multigram scale at 37 °C for 32 h, the desired 6S-enantiomer was obtained in 92% ee. The optical purity of 6S was determined by formation of the Mosher ester and ¹⁹F NMR analysis.^{19,20} The control experiment without the enzyme afforded only a trace amount of acylated product after 48 h at 23 °C. Acetate 7 was readily converted to 2-(S)-1-benzyloxy-3-buten-2-ol (6S) in a threestep sequence involving the following: (1) saponification of 7 with K₂CO₃ in MeOH at 23 °C for 35 min to provide

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SCHEME 2. Synthesis of Dihydrofuranone from d-Glyceraldehyde



2(R)-1-benzyloxy-3-buten-2-ol (6R), (2) Mitsunobu inver $sion^{21}$ of the resulting 2(R)-alcohol with Ph₃P, p-NO₂benzoic acid in the presence of diethylazodicarboxylate at 23 °C for 40 min, and (3) aqueous lithium hydroxide promoted saponification of the resulting benzoate derivative. The 6S-alcohol thus obtained (82% overall in three steps) has shown high optical purity of 81% ee. The represented absolute configurations of the resolved alcohols were assigned on the basis of comparison of optical rotation with the literature data.²² Optically active allylic alcohol 6S was converted to acrylate ester 8 by reaction with acryloyl chloride and Et₃N in CH₂Cl₂ at 0 °C for 10 min. The acrylate ester 8 was isolated in 92% yield after silica gel chromatography. Olefin metathesis of 8 with commercially available Grubbs' second-generation catalyst (4 mol %) in refluxing CH_2Cl_2 for 5 h furnished the α . β -unsaturated γ -lactone **9a** in 98% yield.^{23,24} The overall procedure is quite convenient, and multigram quantities of 5(S)-benzyloxymethyl-2(5H)-furanone have been prepared using this route.

Scheme 2 represents our second route which has provided various protected hydroxymethyl-2(5*H*)-furanone derivatives (**9b**-**f**) for our photochemical studies. Isopylidene-D-glyceraldehyde (**10**) was prepared by cleavage of commercially available diisopropylidene-D-mannitol with sodium periodate as described previously.²⁵ Wittig reaction of **10** with methyl (triphenylphosphoranylidene)acetate in methanol at 0 °C for 2 h afforded a mixture of olefins (*E*/*Z* ratio 1:7.3) in 75% yield. The major *Z*-isomer **11** was separated by silica gel chromatography.²⁶ Exposure of **11** to a catalytic amount of concentrated H₂SO₄ in methanol at 23 °C furnished 5(*S*)-

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SCHEME 3. Photochemical 1,3-Dioxalane Addition to 9a-f and 12



TABLE 1. Results from the Photochemical Reactions of Enones 9a-e

entry	R	Ph ₂ CO (%)	reaction conditions $(T (^{\circ}C))$ time (h))	product	yield (%)	anti/syn (ratio)
1	Bn	10	0 (9)	13a	82	96:4
2	TBDMS	150	20(4.5)	13b	36	76:24
2	TBDMS	10	6 (12)	13b	87	96:4
3	$OCCH_3$	8	6 (6)	13c	91	96:4
4	OCt-Bu	11	6 (5)	13d	93	97:3
5	OCPh	15	6 (3)	13e	80	96:4
6	THP	15	20 (6)	13f	91	96:4
7	Н	10	0 (4)	13g	80	97:3

hydroxymethyl-2(5*H*)-furanone (12) in near-quantitative yield. Alcohol 12 was converted to TBDMS-ether **9b** in quantitative yield. Reaction of **12** with acetyl chloride, pivaloyl chloride, and benzoyl chloride in the presence of pyridine afforded acetate **9c**, pivaloate **9d**, and benzoate **9e**, respectively. Treatment of **12** with dihydropyran in the presence of a catalytic amount of *p*-TsOH furnished THP-ether **9f**.

With various protected enones (9a-f) in hand, we then investigated photochemical conjugate addition of 1,3dioxolane under a variety of reaction conditions (Scheme 3). In a typical experiment, irradiation of enone was carried out in a flask containing enone and a catalytic amount of benzophenone dissolved in degassed 1,3dioxolane from a distance of 10 cm using one 450 W ACE glass medium-pressure mercury lamp at a specified temperature. The reaction was monitored by TLC or by ¹H NMR analysis. After the reaction was completed, the solvent was evaporated and the residue was purified by column chromatorgraphy. Reaction temperature and amount of benzophenone turned out to be critical to the observed stereoselectivity and reaction yield. Optimum results were obtained when irradiation of 9 was carried out in 1,3-dioxolane in the presence of a catalytic amount (15 mol % or less) of benzophenone at a temperature below 20 °C. The results of a variety of substrates are shown in Table 1. As can be seen, the additions are completely regioselective and tolerated a variety of protecting groups. Reaction with unprotected alcohol 12 also proceeded with excellent yield and diastereoselectivity under the reaction conditions.

For synthesis of bis-THF ligand, irradiation of **9a** was carried out in the presence of 15 mol % benzophenone at 0 °C for 9 h. This condition provided dioxolane derivative **13a** in 82% yield as a 96:4 mixture of *anti/syn* ratio (by ¹H and ¹³C NMR analysis). The isomers were separated by silica gel chromatography, and the major *trans* isomer was converted to the bis-THF derivative following the reaction sequence outlined in Scheme 4. Catalytic hydrogenation of **13a** over 10% Pd-C in MeOH afforded alcohol **14** in 89% yield. Reduction of **14** with LAH followed by acid-catalyzed cyclization furnished bis-

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⁽²⁰⁾ The Mosher ester was formed by reaction of Mosher acid and alcohol with DCC in the presence of DMAP. Typically, reaction yields are in the range of 95-98%. Mosher esters of racemic alcohol provided a 1:1 mixture of diastereomers by ¹⁹F NMR, indicating that there was no diastereoselection during esterification process.

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SCHEME 4. Synthesis of Optically Active Bis-tetrahydrofuran



tetrahydrofuran derivative 15 in 77% yield in two steps. Epimeric alcohol 15 has been converted to the desired bis-THF derivative 3 by an oxidation/reduction sequence. TPAP oxidation²⁷ of **15** provided the corresponding ketone which was reduced with NaBH₄ to afford optically active bis-tetrahydrofuranyl alcohol **3** as a single isomer by ¹H and ¹³C NMR analysis. Alcohol 15 has also been converted to 3 by a two-step sequence involving (1) Mitsunobu inversion²¹ with Ph_3P and *p*-nitrobenzoic acid in the presence of diisopropylazodicarboxylate and (2) aqueous lithium hydroxide promoted saponification of the resulting benzoate derivative to provide 3. The photoadduts 13a-g may provide access to other functionalized bis-THF derivatives particularly at the C4 and C5 positions of bis-THF ring through alkylation of lactone or addition to the lactone carbonyl or to the corresponding aldehyde.

Optically active bis-THF ligand 3 was converted to inhibitor 2 as shown in Scheme 5. For the synthesis of inhibitor 2, our plan was to carry out an alkoxycarbonylation²⁸ of isostere amine $4 (X = NH_2)$ and the activated mixed carbonate of 3-hydroxy-bis-tetrahydrofuran. Thus, alcohol 3 was converted to mixed carbonate 16 by reaction with N,N'-disuccinimidyl carbonate in the presence of triethylamine for 5 h at 23 °C. For the synthesis of sulfonamide isostere 4 (X = NH_2), commercially available²⁹ epoxide **17** was reacted with isobutylamine **18** in 2-propanol at reflux to provide the corresponding amino alcohol. Reaction of the resulting amino alcohol with *p*-nitrobenzenesulfonyl chloride in the presence of aqueous NaHCO₃ furnished sulfonamide derivative 19 in 96% yield. Catalytic hydrogenation of 19 over 10% Pd-C in ethyl acetate effected reduction of the nitro group to the corresponding aromatic amine.³⁰ Exposure of the resulting amine to trifluoroacetic acid at 23 °C for 2 h removed the BOC-group and afforded the correspond-





ing diamine. Exposure of the diamine to mixed carbonate 16 in the presence of triethylamine at 23 °C for 6 h provided inhibitor 2 selectively in 85% yield for the three-step sequence.

Conclusion

In conclusion, we have described a convenient synthesis of (3R,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furan. This optically active heterocycle is an important high affinity nonpeptidal P2-ligand for HIV protease inhibitor UIC-94017 (TMC-114) which is undergoing advanced clinical trials. The key synthetic step involves a stereoselective photochemical 1,3-dioxolane addition to 5(S)hydroxymethyl-2(5H)-furanone derivatives. Optically active benzyloxy furanone derivative was conveniently prepared by an immobilized lipase-catalyzed selective acylation of (\pm) -1-(benzyloxy)-3-buten-2-ol followed by a ring-closing olefin metathesis of the resulting acrylate ester with Grubbs' catalyst. The overall synthesis of 3-hydroxyhexahydrofuro[2,3-b]furan is efficient and has potential for scale-up. Furthermore, the current synthesis may provide access to other substituents particularly at the C2, C4, or C5 positions through akylation and carbonyl addition to the photoadduct. Optically active bis-THF so obtained was converted to protease inhibitor 2 (UIC-94017). Design and synthesis of other functionalized 3-hydroxyhexahydrofuro[2,3-b]furan derivatives are in progress.

Experimental Section

1-(Benzyloxy)but-3-en-2-ol ((\pm)-6). To a solution of vinylmagnesium bromide (1 M in THF, 40 mL, 40 mmol) in THF (10 mL) at 0 °C was added benzyloxyacetaldehyde (5) (5 g, 33.3 mmol) dropwise. The mixture was stirred for 10 min at 0 °C, and the reaction was quenched with 20 mL of saturated

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NaHCO₃ solution. The layers were separated, the aqueous layer was extracted with ethyl acetate (3×), and the combined organic extracts were dried over sodium sulfate. Evaporation of solvent under reduced pressure, followed by column chromatography over silica gel (20% EtOAc in hexanes as the eluent), yielded the alcohol (±)-**6** (5.22 g, 88%) as a yellow oil: $R_f = 0.40$ (30% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃) δ 2.79 (bs, 1H), 3.39 (dd, 1H, J = 7.85, 9.6 Hz), 3.55 (dd, 1H, J = 3.35, 9.6 Hz), 4.35 (m, 1H), 4.58 (s, 1H), 5.21 (dt, 1H, J = 1.4, 10.6 Hz), 5.38 (dt, 1H, J = 1.4, 17.4 Hz), 5.84 (m, 1H), 7.30–7.38 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 71.5, 73.4, 74.0, 116.5, 127.9, 128.5, 136.6, 137.8.

(S)-1-(Benzyloxy)-but-3-en-2-ol (6S) and (R)-1-(Benzyloxy)but-3-en-2-oyl Acetate (7). To a solution of alcohol (\pm) -6 (3.55 g, 19.9 mmol) in isopropenyl acetate (45 mL, 400 mmol) and ethylene glycol dimethyl ether (45 mL, 400 mmol) was added immobilized lipase PS-30 (3.6 g) on Celite-545. The mixture was stirred at 37 °C for 32 h and then filtered through Celite. Removal of solvent under reduced pressure, followed by column chromatography over silica gel (10 and 15% EtOAc in hexanes as the eluents), yielded acetate 7 (2.3 g, 49%) as an oil: $R_f = 0.57$ (30% EtOAc in hexanes); $[\alpha]^{23}_{D} - 1.7$ (c 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) & 2.10 (s, 3H), 3.55-3.59 (m, 2H), 4.56 (ABq, 2H, v = 23.2.2, J = 12.2, 26.2 Hz), 5.24 (d, 1H, J = 10.6 Hz), 5.32 (d, 1H, J = 17.3 Hz), 5.50 (m, 1H), 5.84 (m, 1H), 7.25–7.36 (m, 5H); $^{13}\mathrm{C}$ NMR (125 MHz, CDCl_3) δ 21.6, 71.7, 73.6, 73.6, 118.4, 128.1, 128.8, 133.8, 138.3, 170.6; HRMS-ESI (m/z) [M + Na]⁺ calcd for C₁₃H₁₆O₃ 243.0997, found 243.0999. Alcohol 6S (1.9 g, 49%) was obtained as a yellow oil: $R_f = 0.40$ (30% EtOAc in hexanes); $[\alpha]^{23}$ _D -3.2 (c 1.4, CHCl₃); HRMS-ESI (m/z) [M + Na]⁺ calcd for C₁₁H₁₄O₂ 201.0891, found 201.0883.

(*R*)-1-(Benzyloxy)but-3-en-2-ol (6*R*). To a solution of acetate 7 (3.7 g, 16.9 mmol) in methanol (20 mL) was added K_2CO_3 (7 g, 50.6 mmol). The mixture was stirred at room temperature for 35 min. Methanol was then removed under reduced pressure. The resultant solid residue was dissolved in ethyl acetate, washed with saturated NH₄Cl solution and brine, and dried over sodium sulfate. Removal of ethyl acetate under reduced pressure yielded alcohol 6*R* (3 g, 100%) as a yellow oil: $R_f = 0.40$ (30% EtOAc in hexanes); [α]²³_D 2.87 (*c* 1.3, CHCl₃); HRMS-ESI (*m*/*z*) [M + Na]⁺ calcd for C₁₁H₁₄O₂ 201.0891, found 201.0883.

(S)-1-(Benzyloxy)but-3-en-2-ol (6S) from 7. To a solution of alcohol 6*R* (2 g, 11.2 mmol), triphenylphosphine (5.88 g, 22.4 mmol), and 4-nitrobenzoic acid (2.81 g, 16.8 mmol) in benzene (35 mL) was added at room temperature diisopropyl azodicarboxylate (4.35 mL, 22.4 mmol) dropwise. The mixture was stirred for 40 min, and the solvent was removed under reduced pressure. The crude ester was dissolved in a mixture of MeOH/ H₂O (20 mL) in a ratio of 4:1 and reacted with LiOH (1.64 g, 39.3 mmol) at room temperature. The mixture was stirred for 2 h, and after this period, the solvents were removed under reduced pressure. The residue was purified by column chromatography over silica gel (15% EtOAc in hexanes as the eluent) to yield alcohol 6S (1.64 g, 82%) as a yellow oil: $R_f =$ 0.40 (30% EtOAc in hexanes); [α]²³_D -2.82 (c 1.4, CHCl₃).

(S)-1-(Benzyloxy)but-3-en-2-yl Acrylate 8. To a solution of alcohol 6S (1 g, 5.61 mmol) in CH₂Cl₂ (20 mL) at 0 °C were added acryloyl chloride (0.7 mL, 8.41 mmol) and Et₃N (1.56 mL, 11.2 mmol). The mixture was stirred for 10 min, and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel using 15% EtOAc in hexanes as the eluent to provide acrylate 8 (1.19 g, 92%) as a colorless oil: $R_f = 0.57$ (30% EtOAc in hexanes); [α]²³_D -5.7 (c 1.09, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 3.59-3.65 (m, 2H), 4.55 (A of AB, J = 12.2 Hz), 4.61 (B of AB, J = 12.2 Hz), 5.25 (d, 1H, J = 10.6 Hz), 5.33 (d, 1H, J = 10.4, 17.3 Hz), 6.44 (dd, 1H, J = 1.3, 17.4 Hz), 7.27-7.36 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 71.6, 73.6, 73.8, 118.5, 128.1, 128.9, 131.5, 133.6,

138.3, 165.8; HRMS-ESI (m/z) $\rm [M+Na]^+$ calcd for $\rm C_{14}H_{16}O_3$ 255.0997, found 255.0994.

(5S)-5-(Benzyloxymethyl)-5*H*-furan-2-one 9a. To a solution of acrylate 8 (1.87 g, 8.05 mmol) in CH₂Cl₂ (700 mL) was added second-generation Grubbs' catalyst (4 mol %, 170 mg, 0.322 mmol). The resulting reaction mixture was refluxed for 5 h. After this period, the solvent was removed under reduced pressure and the residue was chromatographed over silica gel (30% EtOAc in hexanes as the eluent) to yield furanone 9a (1.62 g, 98%) as a brown oil: $R_f = 0.15$ (30% EtOAc in hexanes); $[\alpha]^{23}_D - 81.3$ (*c* 1.09, MeOH); ¹H NMR (500 MHz, CDCl₃) δ 3.66 (dd, 1H, J = 5.0, 10.4 Hz), 3.71 (dd, 1H, J = 5.0, 10.4 Hz), 4.57 (s, 2H), 5.17 (m, 1H), 6.16 (dd, 1H, J = 1.9, 5.7 Hz), 7.29–7.37 (m, 5H), 7.48 (dt, 1H, J = 1.25, 5.7 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 69.9, 74.2, 82.6, 123.0, 128.4, 128.9, 137.7, 154.3, 173.2; HRMS-ESI (*m*/*z*) [M + Na]⁺ calcd for C₁₂H₁₂O₃ 227.0684, found 227.0685.

(4S)-Methyl 3-(2,2-Dimethyl-1,3-dioxolan-4-yl)acrylate (11). To a solution of 2,3-O-isopropylidene-D-glyceraldehyde (4.2 g, 32.3 mmol) in MeOH at 0 °C was added methyl (triphenylphosphoranylidene)acetate (11.3 g, 33.9 mmol). The reaction mixture was allowed to stir for 2 h at 0 °C. After this period, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in a mixture (3:7) of ether and hexanes and refluxed for 30 min. The solvent was decanted; the process was repeated six times. The combined cooled extracts were filtered, and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel using 7 and 9% EtOAc in hexanes as the eluents to yield acrylate **11** (3.94 g, 66%) as yellow oils: $R_f = 0.56 (15\%)$ EtOAc in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 1.34 (s, 3H), 1.40 (s, 3H). 3.55 (dd, 1H, J = 8.0, 15.0 Hz), 3.67 (s, 3H), 4.31 (dd, 1H, J = 8.0, 15.0 Hz), 5.37 (m, 1H), 5.79 (dd, 1H, J = 1.5)11.0 Hz), 6.28 (dd, 1H, J = 6.0, 11.0 Hz); ¹³C NMR (125 MHz, CDCl₃) & 25.4, 26.6, 51.7, 69.39, 73.6, 109.7, 120.3, 149.6, 166.1.

(S)-5-Hydroxymethyl-5H-furan-2-one (12). To a solution of (4'S)-methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (11) (3.7 g, 19.9 mmol) in MeOH was added a catalytic amount of concentrated sulfuric acid (25 μ L of 10%). The mixture was stirred at 23 °C for 2 h. After this period, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed over silica gel (7% MeOH in CHCl₃ as the eluents) to yield the title compound (2.2 g, 97%) as a white solid: $R_f = 0.30$ (100% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃) δ 3.71 (dd, 1H, J = 4.8., 12.3 Hz), 3.77 (bs, 1H), 3.91 (dd, 1H, J = 3.82, 12.34 Hz), 5.12 (m, 1H), 6.16 (dd, 1H, J = 2.1, 5.8 Hz), 7.50 (dd, 1H, J = 1.3, 5.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 61.9, 84.5, 122.6, 154.5, 173.9.

(5S)-5-(tert-Butyldimethylsilanyloxymethyl)-5H-furan-**2-one 9b.** To a solution of (5S)-hydroxymethyl-5*H*-furan-2-one **12** (199 mg, 1.74 mmol) and imidazole (178 mg, 2.61 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $\mathit{tert}\text{-butyldimethylsilyl}$ chloride (342 mg, 2.27 mmol). The resulting mixture was stirred for 30 min at 0 °C and then at 23 °C for 30 min. The reaction was quenched by addition of 40 mL of water. The layers were separated; the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over sodium sulfate. Evaporation of the solvent followed by column chromatorgraphy over silica gel (20% ethyl acetate in hexanes as the eluent) yielded the title compound (398 mg, 99%) as a colorless solid: $R_f = 0.24$; $[\alpha]^{23}_{D} - 137$ (*c* 0.9, CHCl₃); IR (neat) 2929, 1755, 1256, 837 cm $^{-1};$ $^1\mathrm{H}$ NMR (500 MHz, CDCl_3) δ 0.06 (s, 6H), 0.87 (s, 9H), 3.79 (dd, 1H, J = 5.5, 10.8 Hz), 3.92 (dd, 1H, J = 4.5, 10.8 Hz), 5.05 (m, 1H), 6.16 (dd, 1H, J = 1.2, 4.5 Hz), 7.49 (dd, 1H, J = 1.2, 5.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 5.1, 18.6, 26.1, 63.3, 83.8, 122.9, 154.8, 173.4; HRMS-ESI $(\ensuremath{\textit{m/z}})\,[\ensuremath{\textit{M}}-\ensuremath{\textit{H}}]^+$ calcd for $C_{11}H_{20}O_3Si$ 251.1079, found 251.1080.

(5S)-5-(Acetyloxymethyl)-5H-furan-2-one (9c). To a solution (5S)-hydroxymethyl-5H-furan-2-one (12) (1.01 g, 8.87 mmol) in dry pyridine (50 mL) at 0 °C was added a solution of acetyl chloride (0.63 mL, 8.87 mmol) in CH₂Cl₂ (10 mL). The resulting mixture was stirred for 1 h at 0 °C. After this period,

the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in CH₂Cl₂ (50 mL) and washed with saturated sodium bicarbonate solution (50 mL). The layers were separated; the aqueous layer was extracted with CH₂Cl₂ (3×). The combined organic extracts were dried over sodium sulfate. Evaporation of the solvent followed by column chromatorgraphy over silica gel (50% ethyl acctate in hexanes as the eluent) yielded the title compound (1.27 g, 92%) as a colorless solid: $R_f = 0.31$; (α]²³_D - 134.5 (*c* 1.3, CHCl₃); IR (neat) 1746, 1367, 1218, 767 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.05 (s, 3H), 4.32 (m, 2H), 5.23 (m, 1H), 6.20 (dd, 1H, J = 2.2, 5.8 Hz), 7.43 (dd, 1H, J = 1.6, 5.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 20.6, 62.6, 80.7, 123.3, 152.3, 170.5, 172.2; HRMS-ESI (m/z) [M - H]⁺ calcd for C₇H₈O₄ 179.0320, found 179.0323.

(5S)-5-(Pivaloyloxymethyl)-5H-furan-2-one (9d). To a solution of (5S)-hydroxymethyl-5H-furan-2-one (12) (101 mg, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added pyridine (1 mL, 0.98 mmol) and a solution of pivaloyl chloride (120 μ L, 0.97 mmol) in CH₂Cl₂ (2 mL). The resulting mixture was stirred for 3 h at 0 °C, and the reaction mixture was allowed to stir at 23 °C for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in CH₂Cl₂ (10 mL). The organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate. Evaporation of the solvent followed by column chromatorgraphy over silica gel (40% ethyl acetate in hexanes as the eluent) yielded the title compound (143 mg, 81%) as a colorless solid: $R_f = 0.20$; $[\alpha]^{23}_D - 138 (c \ 1.3, CHCl_3)$; IR (neat) 3056, 1756, 1730, 1616, 1172 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.16 (s, 9H), 4.36 (d, 2H, J = 4.2 Hz), 5.23 (dd, 1H, J = 1.8, 4.2 Hz), 6.18 (dd, 1H, J = 1.8, 5.4 Hz), 7.42 (dd, 1H, J = 1.8, 5.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 26.8, 38.6, 61.7, 80.8, 123.0, 152.2, 172.0, 177.8. HRMS-ESI (m/z) [M - H]⁺ calcd for C₁₀H₁₄O₄ 221.0790, found 221.0779.

(5S)-5-(Benzoyloxymethyl)-5H-furan-2-one (9e). To a solution of (5S)-hydroxymethyl-5H-furan-2-one (12) (94 mg, 0.82 mmol) in dry pyridine (10 mL) at 0 °C was added a solution of benzoyl chloride (96 μ L, 0.82 mmol) in CH₂Cl₂ (2 mL). The resulting mixture was stirred at 0 °C for 1 h. After this period, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL). Saturated sodium bicarbonate solution (5 mL).was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane $(3\times)$, and the combined organic extracts were dried over sodium sulfate. Evaporation of the solvent followed by column chromatorgraphy over silica gel (40% ethyl acetate in hexanes as the eluent) yielded the title compound (154 mg, 86%) as a colorless solid: $R_f = 0.30$; $[\alpha]^{23}_{D}$ -119.1 (c 0.8, CHCl₃); IR (neat) 1787, 1762, 1772, 1271, 771 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.57 (dd, 2H, J = 4.2, 9.0 Hz), 5.34 (m, 1H), 6.17 (dd, 1H, J = 1.8, 5.4 Hz), 7.41 (m, 2H), 7.51 (m, 2H), 7.93 (dd, J = 5.1, 6.9 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 62.6, 80.7, 123.1, 128.3, 128.8, 129.4, 133.3, 152.5, 165.7, 172.1; HRMS-ESI (m/z) [M - H]⁺ calcd for C₁₀H₁₀O₄ 241.0477, found 241.0483.

(5S)-5-(Tetrahydropyran-2-yloxymethyl)-5H-furan-2one (9f). To a solution of (5S)-hydroxymethyl-5H-furan-2-one (12) (100 mg, 0.88 mmol) in CH₂Cl₂ (10 mL) at 23 °C were added dihydropyran (88 µL, 0.97 mmol) and p-tolunesolfonylacid (10 mg, 0.053 mmol). The resulting mixture was stirred at 23 °C for 8 h. After this period, the reaction was quenched with saturated sodium bicarbonate solution (5 mL). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over sodium sulfate. Evaporation of the solvent followed by column chromatorgraphy over silica gel (60% ethyl acetate in hexanes as the eluent) yielded the title compound (136 mg, 78%) as a colorless solid: $R_f = 0.23$, $[\alpha]^{23}_D - 71$, c 0.7, CHCl₃. IR (neat) 3070, 1240, 1753, 1618, 1154, 832 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.32-1.55 (m, 4H), 1.56-1.80 (m, 2H), 3.41-3.51 (m, 1H), 3.58-3.62 (m, 1H), 3.67-3.81 (m, 1H), 3.84-3.91 (m, 1H), 4.51-4.53 (m,0.5H), 4.56-4.58 (m, 0.5H), 5.12–5.16 (m, 1H), 6.09 (dd, 1H, J=5.9, 8.0 Hz), 7.47 (dd, 1H, J=1.1, 5.9 Hz); $^{13}\mathrm{C}$ NMR (125 MHz, CDCl₃) δ major diastereomer 19.4, 25.6, 30.6, 62.4, 66.9, 82.4, 99.3, 122.8, 154.3, 173.2, minor diastereomer 19.6, 25.6, 30.6, 62.7, 67.3, 82.8, 99.7, 122.9, 154.6, 173.3; HRMS-ESI (m/z) [M – H]^+ calcd for C_{10}H_{14}O_4 221.0790, found 221.0780.

General Procedure for the Photoaddition of 1,3-Dioxolane to the Enones 9a-f. A solution of the enone 9a-fand benzophenone in 1,3-dioxolane was degassed for 1 h by bubbling through a stream of argon. The flask was placed in a water-cooled cooling mantel. After the solution was cooled to the desired temperature, it was then irradiated from a distance of 10 cm using a 450 W ACE glass medium-pressure mercury lamp. After the reaction was completed, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography.

(4S,5S)-5-(Benzyloxymethyl)-4-(1,3-dioxolan-2-yl)dihydrofuran-2-one (13a). A solution of furanone 9a (1.2 g, 5.88 mmols) and benzophenone (108 mg, 0.59 mmols) in 1,3dioxolane (108 mL) was irradiated for 9 h at 0 °C. The progress of this reaction was monitored by ¹H NMR. Upon completion of the reaction, solvent was removed under reduced pressure and the resdue was purified by column chromatography on silica gel (35% EtOAc in hexanes as the eluent) to provide the title compound **13a** (1.34 g, 82%) as a clear oil: $R_f = 0.14$ (30%) EtOAc in hexanes); $[\alpha]^{23}_D$ 16.5 (c 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.50 (dd, 1H, J = 3.9, 16.9 Hz), 2.70–2.79 (m, 2H), 3.58 (dd, 1H, J = 3.5, 10.75 Hz), 3.75 (dd, 1H, J = 2.8, 10.8 Hz), 3.87-3.92 (m, 2H), 3.97-4.00 (m, 2H), 4.51 (d, 1H, J = 11.9 Hz), 4.57–4.61 (m, 2H), 4.88 (d, 1H, J = 3.6 Hz), 7.26-7.36 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 30.4, 40.5, 65.8, 71.7, 74.0, 79.5, 104.1, 128.0, 128.9, 138.1, 176.8; HRMS-ESI (m/z) [M + Na]⁺ calcd for C₁₅H₁₈O₅ 301.1052, found 301.1047.

(4S,5S)-5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(1,3dioxolan-2-yl)dihydrofuran-2-one (13b). A solution of (5S)-5-(*tert*-butyldimethylsilanyloxymethyl)-5H-furan-2-one (9b) (228 mg, 1 mmol) and benzophenone (18 mg, 0.1 mmol) in 1,3dioxolane (200 mL) was irradiated at 20 °C for 5 h. The title compound (285 mg, 94%) was obtained as a colorless solid after silica gel chromatography (30% ethyl acetate in hexanes): R_f = 0.35; $[\alpha]^{23}_{D}$ 18.3 (*c* 1.3, CHCl₃); IR (neat) 2953, 2857, 1778, 1125 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.05 (s, 6H), 0.87 (s, 9H), 2.45 (dd, 1H, *J* = 4.2, 17.7 Hz), 2.68 (d, 1H, *J* = 17.7 Hz), 2.72–2.79 (m, 1H), 3.65 (dd, 1H, *J* = 2.7, 11.4 Hz), 3.86–3.91 (m, 3H), 3.97–4.01 (m, 2H), 4.50 (m_c, 1H), 4.88 (d, 1H, *J* = 3.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 5.5, 18.2, 25.8, 30.1, 39.7, 64.7, 65.4, 65.5, 80.2, 103.9, 176.6.

(4S,5S)-5-(Acetyloxymethyl)-4-(1,3-dioxolan-2-yl)dihydrofuran-2-one (13c). A solution of (5S)-5-(acetyloxymethyl)-5H-furan-2-one 9c (1.20 g, 7.7 mmol) and benzophenone (107 mg, 0.59 mmol) in 1,3-dioxolane (230 mL) was irradiated at 0 °C for 8.5 h. The title compound (1.63 mg, 92%) was obtained as an oil after silica gel chromatography (50% ethyl acetate in hexanes): $R_f = 0.32$; $[\alpha]^{23}_D$ 36.2 (c 1.3, CHCl₃); IR (neat) 1780, 1745, 1216, 759 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.08 (s, 3H), 2.52 (dd, 1H, J = 10.4, 21.7 Hz), 2.61–2.66 (m, 2H), 3.84–3.88 (m, 2H), 3.94–3.98 (m, 2H), 4.09 (dd, 1H, J = 5.0, 12.3 Hz), 4.32 (dd, 1H, J = 2.9, 12.3 Hz), 4.62 (m, 1H), 4.87 (d, 1H, J = 3.6 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 21.1, 30.2, 40.5, 65.7, 65.8, 65.9, 77.8, 103.5, 170.9, 175.9.

(4S,5S)-5-(Pivaloyloxymethyl)-4-(1,3-dioxolan-2-yl)dihydrofuran-2-one (13d). A solution of (5S)-5-(pvaloyloxymethyl)-5*H*-furan-2-one (9d) (29 mg, 0.15 mmol) and benzophenone (3 mg, 0.016 mmol) in 1,3-dioxolane (20 mL) was irradiated at 0 °C for 1.5 h. The title compound (37 mg, 93%) was obtained as an oil after silica gel chromatography (40% ethyl acetate in hexanes): $R_f = 0.21$; [α]²³_D 23.8 (c 1.0, CHCl₃); IR (neat) 1785, 1740, 1210, 740 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 1.21 (s, 9H), 2.57–2.60 (m, 1H), 2.67–2.75 (m, 2H), 3.91–3.93 (m, 2H), 4.01–4.04 (m, 2H), 4.37 (dd, 1H, J = 4.2, 12.2 Hz), 4.38 (dd, 1H, J = 2.9, 12.2 Hz), 4.69 (m_c, 1H), 4.92 (d, 1H, J=3.6 Hz); $^{13}\mathrm{C}$ NMR (100 MHz, CDCl_3) δ 27.1, 29.8, 38.7, 37.7, 65.3, 65.4, 65.6, 77.4, 103.3, 175.5, 178.0.

(4S,5S)-5-(Benzoyloxymethyl)-4-(1,3-dioxolan-2-yl)dihydrofuran-2-one (13e). A solution of (5S)-5-(benzoyloxymethyl)-5*H*-furan-2-one (9e) (180 mg, 0.825 mmol) and benzophenone (22.5 mg, 0.123 mmol) in 1,3-dioxolane (110 mL) was irradiated at 20 °C for 3 h. The title compound (193 mg, 80%) was obtained as an oil after silica gel chromatography (40% ethyl acetate in hexanes): $R_f = 0.29$; [α]²³_D 35.2 (*c* 1.2, CHCl₃); IR (neat) 2360, 2342, 1779, 1721, 1272, 1118 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.53 (d, 1H *J* = 11.6 Hz), 2.62– 2.73 (m, 2H), 3.83 (m_c, 2H), 3.94 (m_c, 2H), 4.37 (dd, 1H, *J* = 5.1, 12.3 Hz), 4.53 (dd, 1H, *J* = 2.9, 12.3 Hz), 4.74 (ddd, 1H, *J* = 2.7, 7.9 Hz), 7.49 (dd, 1H, *J* = 1.0, 7.7 Hz), 7.92 (dd, 2H, *J* = 1.0, 7.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 29.8, 40.1, 65.4, 65.5, 66.0, 77.6, 103.1, 128.5, 129.3, 129.6, 133.3, 166.0, 175.6.

(4S,5S)-4-(1,3-Dioxolan-2-yl)-5-(tetrahydropyran-2yloxymethyl)dihydrofuran-2-one (13f). A solution of (5S)-5-(tetrahydropyran-2-yloxymethyl)-5H-furan-2-one (9f) (136 mg, 0.67 mmol) and benzophenone (19 mg, 0.1 mmol) in 1,3dioxolane (100 mL) was irradiated at 20 °C for 6 h. The title compound (170 mg, 91%) was obtained as an oil after silica gel chromatography (60% ethyl acetate in hexanes): $R_f = 0.25$; [α]²³_D 47 (c 1.0, CHCl₃); IR (neat) 2960, 2877, 1780, 1131, 851 cm^1; ¹H NMR (300 MHz, CDCl₃) δ 1.38–1.82 (m, 6H), 2.40– 2.46 (m, 1H), 2.60-2.75 (m, 2H), 3.39-3.48 (m, 1H), 3.61-3.70 (m, 1H), 3.75-3.81 (m, 2H), 3.84-3.87 (m, 2H), 3.93-3.98 (m, 2H), 4.53-4.63 (m, 2H), 4.86-4.89 (m, 1H). ¹³C NMR $(75 \text{ MHz}, \text{CDCl}_3) \delta$ major diastereomer 18.7, 25.2, 29.9, 30.0, 40.1, 61.5, 64.7, 65.3, 68.3, 79.0, 98.2, 103.6, 176.5, minor diastereomer 19.2, 25.2, 30.2, 30.2, 40.1, 62.2, 65.1, 65.5, 68.8, 79.1, 99.1, 103.7, 176.7.

(4S,5S)-4-(1,3-Dioxolan-2-yl)-5-hydroxymethyldihydrofuran-2-one (13g). A solution of (5S)-5-(hydroxymethyl)-5Hfuran-2-one (154 mg, 1.35 mmol) and benzophenone (25 mg, 0.135 mmol) in 1,3-dioxolane (100 mL) was irradiated at 0 °C for 4 h. Upon completion of the reaction, solvent was removed under reduced pressure, followed by column chromatography on silica gel (5% MeOH in CHCl₃ as the eluent), yielding the title compound **13g** (205 mg, 80%): $R_f = 0.28$ (5% MeOH in CHCl₃); [α]²⁵_D 21.8 (*c* 1.02, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.50 (dd, 1H, J = 6.0, 17.5 Hz), 2.69 (dd, 1H, J = 9.5, 17.5 Hz), 2.73–2.78 (m, 1H), 3.00 (bs. 1H), 3.64 (dd, 1H, J = 4.0, 12.5 Hz), 3.86–3.91 (m, 3H), 3.96–3.99 (m, 2H), 4.50–4.52 (m, 1H), 4.84 (d, 1H, J = 4 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 30.2, 39.8, 63.8, 65.4, 65.5, 80.9, 103.6, 176.8.

(4S,5S)-4-(1,3-Dioxolan-2-yl)-5-hydroxymethyldihydrofuran-2-one (14). To a solution of dihydrofuranone 13a (0.5 g, 1.79 mmol) in MeOH (30 mL) was added Pd/C (25 mg). The mixture was stirred at 23 °C under an H₂ balloon for 24 h. The reaction mixture was filtered through a pad of Celite. Removal of solvent under reduced pressure, followed by column chromatography over silica gel (35% EtOAc in hexanes as the eluent), yielded compound 14 (301 mg, 89%) as an oil: $R_f =$ 0.28 (50% EtOAc in hexanes); [α]²³_D 22 (c 1.32, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.54 (dd, 1H, J = 3.9, 12.4 Hz), 3.88–3.95 (m, 3H), 3.97–4.02 (m, 2H), 4.53 (m, 1H), 4.91 (d, 1H, J = 3.9Hz); ¹³C NMR (125 MHz, CDCl₃) δ 30.7, 40.1, 64.4, 65.8, 81.1, 103.9, 176.8; HRMS-ESI (m/z) [M + Na]⁺ calcd for C₈H₁₂O₅ 211.0582, found 211.0584.

(3S,3aS,6aR)-3-Hydroxyhexahydrofuro[2,3-b]furan (15). To a solution of lithium aluminum hydride (76 mg, 1.98 mmols) in THF (10 mL) at 0 °C was added lactone 14 (275 mg, 1.46 mmol) in THF (30 mL) in a dropwise manner over a period of 3 min. The resulting mixture was stirred for 4 h at 0 °C. The reaction was quenched with a saturated aqueous sodium sulfate solution at 0 °C. The solvent was then decanted, and the remaining residue was washed successively with THF (3×), EtOAc (3×), and CHCl₃ (3×). The combined organic extracts was concentrated under reduced pressure to provide

 $(2S,3S)\mbox{-}3-(1,3\mbox{-}dioxolan\mbox{-}2\mbox{-}yl)\mbox{pentane-}1,2,5\mbox{-}triol$ which was immediately used in the next reaction.

The above triol was dissolved in a mixture (5:1) of THF/ H₂O (8 mL). The resulting solution was acidified at 23 °C to pH 2–3 with 1 N hydrochloric acid, and the solution was stirred for 40 h. After this period, benzene was added, and the solvents were removed under reduced pressure. The residure was purified by column chromatography over silica gel (5% MeOH in CHCl₃ as the eluent) to furnish **15** (145 mg, 77%): $R_f = 0.40$ (15% MeOH in CHCl₃); $[\alpha]^{23}_{D} - 25.1$ (*c* 1.05, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.67 (m, 1H), 2.13 (m, 1H), 2.31 (bs, 1H), 2.79 (m, 1H), 3.80–3.88 (m, 3H), 3.95 (dd, 1H, J = 3.2, 10.3 Hz), 4.20 (d, 1H, J = 3.1 Hz), 5.86 (d, 1H, J =4.9 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 29.2, 52.4, 68.3, 75.6, 78.2, 109.2; HRMS-ESI (*m/z*) [M + H]⁺ calcd for C₆H₁₀O₃ 131.0708, found 131.0709.

(3R,3aS,6aR)-3-Hydroxyhexahydrofuro[2,3-b]furan (3). To a mixture of (3S,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furan 15 (440 mg, 3.38 mmol), 4-methylmorpholino-N-oxide (599 mg, 5.11 mmol), and 4 Å molecular sieves (2 g) in CH₂Cl₂ (30 mL) was stirred for 20 min at 23 °C. Tetrapropylammonium perruthenate (36 mg, 0.10 mmol) was added at 23 °C, and the resulting mixture was stirred for 10 min. The reaction mixture was filtered through a short silica gel column and was eluted with CH₂Cl₂. Evaporation of the solvent gave a residue which was chromatorgraphed over silica gel (40% ethyl acetate in hexanes as the eluent) to provide the corresponding ketone (409 mg, 94%) as an amorphous solid: $R_f = 0.3$; $[\alpha]^{23}_{\rm D} - 126.6$ (c 0.8, CHCl₃); IR (neat) 1758, 1658, 1023 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.23 (m_c, 1H), 2.96 (dd, 1H, J = 6.8 Hz, J =6.8 Hz), 3.79 (m_c, 1H), 3.99 (m, 1H), 4.11 (s, 2H), 6.02 (d, 1H, J = 5.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 30.4, 49.6, 67.7, 71.7, 107.9, 215.5.

To a solution of the above ketone (250 mg, 1.95 mmol) in ethanol (25 mL) was added sodium borohydride (89 mg, 2.35 mmol) at -18 °C. The reaction mixture was stirred at -18 °C for 2.5 h. The reaction was quenched with saturated ammonium chloride solution, and the mixture was warmed to room temperature. The mixture was concentrated under reduced pressure, and the residue was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate $(3 \times)$ and a solution of 70% CHCl₃/20% MeOH/10% $H_2O(3\times)$. The combined organic extracts were dried over sodium sulfate. Evaporation of the solvent gave a residue which was chromatographed over silica gel (7% methanol in chloroform as the eluent) to furnish compound **3** (178 mg, 70%) as an oil: $R_f = 0.3$; $[\alpha]^{23}_{\rm D} - 12.4$ (c 1.3, MeOH); IR (neat) 2951, 1641, 1347, 1211 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.85 (m_c, 1H), 1.94 (bs, 1H), 2.27 (m_c, 1H), 2.84 (m_c, 1H), 3.63 (dd, 1H, J = 7.1, 9.2 Hz), 3.89 (m_c, 1H), $3.97 (m_c, 1H), 4.43 (dd, 1H, J = 6.8, 14.5 Hz), 5.68 (d, 1H, J = 6.8, 14.5 Hz)$ J = 5.2 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 25.3, 47.0, 70.3, 71.3, 73.5, 109.9; HRMS-ESI (m/z) [M - H]⁺ calcd for C₆H₉O₃129.0552, found 129.0543.

(3*R*,3a*S*,6a*R*)-3-Hydroxyhexahydrofuro[2,3-*b*]furan (3) (by Mitsunobu Inversion). To a stirred solution of the alcohol 15 (400 mg, 3.07 mmol), triphenylphosphine (1.6 g, 61.4 mmol), and *p*-nitrobenzoic acid (770 mg, 4.61 mmol) in dry benzene (30 mL) at 23 °C was added diisoproylazodicarboxylate (DIAD, 1.2 mL, 6.14 mmol). The resulting mixture was stirred at that temperature for 1.5 h. After this period, the mixture was concentrated under reduced pressure, and the residue was dissolved in a mixture (4:3:1) of MeOH/Et₃N/H₂O (24 mL) and treated with LiOH (450 mg, 10.7 mmol). The reaction mixture was stirred at 23 °C for 2 h. The mixture was concentrated under reduced pressure and the residue was chromatographed over silica gel to provide the title compound 3 (326 mg, 82%) as an oil: $[\alpha]^{23}_{\rm D} -12.4$ (*c* 1.16, MeOH).

(3*R*,3a*S*,6a*R*)-3-Hydroxyhexahydrofuro[2,3-b]furanyl Succinimidyl Carbonate (16). A solution of (3*R*,3a*S*,6a*R*)-3-Hydroxyhexahydrofuro[2,3-b]furan 3 (100 mg, 0.77 mmol), *N*,*N*'-disuccinimidyl carbonate (295 mg, 1.15 mmol), and triethylamine (215 μ L, 1.54 mmol) in acetonitrile (3 mL) was stirred at 23 °C for 7 h. After this period, the reaction mixture was concentrated under reduced pressure, and the residue was treated with saturated aqueous sodium bicarbonate (4 mL). The resulting mixture was extracted with EtOAc $(3\times)$. The combined organic extracts were dried over sodium sulfate. Evaporation of the solvent gave a residue which was chromatorgraphed over silica gel (1% MeOH in CHCl₃ as the eluent) to yield mixed carbonate 16 (135 mg, 66%) as a white solid: mp 122–125 °C; $R_f = 0.62$ (10% MeOH in CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.93-2.15 (m, 1H), 2.10-2.16 (m, 1H), 2.84 (s, 4H), 3.09-3.15 (m, 1H), 3.89-3.97 (m, 2H), 4.01 (, dt, 1H, J = 2.3, 8.4 Hz), 4.09 (dd, 1H, J = 6.0, 10.5 Hz), 5.23 (td, 1H, J = 8.5, 6.0 Hz), 5.73 (d, 1H, J = 5.0 Hz); ¹³C NMR (125) MHz, CDCl₃) δ 25.5, 25.9, 45.1, 69.7, 70.1, 79.7, 109.2, 151.2, 168.5.

(1S,2R)-Benzyl-3-[isobutyl(4-nitrobenzenesulfonyl)amino]-2-hydroxypropyl]carbamic Acid tert-Butyl Ester (19). To a stirred solution of *tert*-butyl[S(R,R)]-(-)-(1-oxiranyl-2-phenylethyl)carbamate (200 mg, 0.76 mmol) in 2-propanol (6 mL) at 23 °C was added isobutylamine (340 µL, 4.55 mmol). The resulting mixture was heated at reflux for 6 h. After this period, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (7% MeOH in CHCl₃ as the eluent) to provide the corresponding amine (268 mg, 99%) as a white solid: mp 145 °C dec; $R_f = 0.35$ (10% MeOH in CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.95 (d, 3H, J = 4.3 Hz), 0.96 (d, 3H, J = 4.3 Hz), 1.35 (s, 9H), 1.85-1.89 (m, 1H), 2.44 (dd, 1H), J = 7.05, 11.7 Hz), 2.57 (dd, 1H, J = 6.6, 11.4 Hz), 2.76 (dd, 1H, J = 5.85, 12.35 Hz), 2.84 (dd, 1H, J = 3.1, 12.4 Hz), 2.90 (dd, H1, J = 7.85, 3.8 Hz), 3.04 (dd, 1H, J = 4.5, 14.2 Hz),3.48-3.53 (m, 1H), 3.84-3.88 (m, 1H), 4.69 (d, 1H, J = 8.8Hz), 7.20–7.33 (m, 5H); $^{13}\mathrm{C}$ NMR (125 MHz, CDCl₃) δ 20.9, 20.9, 28.1, 28.7, 36.9, 52.2, 54.1, 57.9, 70.7, 80.3, 126.9, 128.9, 130.0, 137.8, 156.8; HRMS-ESI (m/z) [M + H]⁺ calcd for C₁₉H₃₂N₂O₃ 337.2491, found 337.2501.

To a stirred solution of above amine (92 mg, 0.273 mmol) in a mixture of $CH_2Cl_2\,(5\mbox{ mL})$ and saturated aqueous sodium bicarbonate (5 mL) at 23 °C was added 4-nitrobenzenesulfonyl chloride (90 mg, 0.409 mmol). The resulting mixture was stirred at 23 °C for 12 h. The mixture was then extracted with CH₂Cl₂ and dried over anhydrous Na₂SO₄. Removal of solvent under reduced pressure, followed by column chromatography over silica gel (3% EtOAc in CHCl₃ as the eluent), yielded compound 19 (140 mg, 96%) as a white amorphous solid: mp 166.5–168.5 °C; $R_f = 0.49$ (10% EtOAc in CHCl₃); ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3) \delta 0.86 \text{ (d, 3H, } J = 6.1 \text{ Hz}), 0.87 \text{ (d, 3H, } J =$ 6.1 Hz), 1.36 (s, 9H), 1.84-1.92 (m, 1H), 2.86-2.95 (m, 2H), 2.98 (d, 2H, J = 7.6 Hz), 3.19 (d, 2H, J = 5.7 Hz), 3.75–3.82 (m, 2H), 4.64 (d, 1H, J = 8.0 Hz), 7.22–7.32 (m, 5H), 7.95 (d, 2H, J = 8.8 Hz), 8.32 (d, 2H, J = 8.8 Hz); ¹³C NMR (125 MHz, CDCl₃) & 19.8, 19.9, 26.9, 28.2, 35.6, 52.5, 55.2, 57.5, 72.2, 80.1, 124.3, 126.7, 128.6, 129.4, 137.5, 144.9, 149.9, 156.4; HRMS-ESI (m/z) [M + Na]⁺ calcd for C₂₅H₃₅N₃O₇S₁ 544.2093, found 544.2083.

(1S,2R,3'R,3'aS,6'aR)-[3'-Hexahydrofuro[2,3-b]furanyl-[3-(4-aminobenzenesulfonyl)isobutylamino]-1-benzyl-2-hydroxypropyl]carbamate (2) (UIC-94017). To a solution of compound 19 (64 mg, 0.123 mmol) in EtOAc (10 mL) was added Pd/C (7 mg). The mixture was stirred at 23 °C under an H₂-filled balloon for 11 h. The reaction mixture was filtered over Celite, and the filter cake was washed with EtOAc. Removal of solvent under reduced pressure, followed by column chromatography on silica gel (7% EtOAc in CHCl₃ as the eluent) afforded the corresponding aromatic amine (61 mg, 95%) as a white solid: mp 60–63 °C; $R_f = 0.16$ (10% EtOAc in CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.86 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz), 1.34 (s, 9H), 1.80 - 1.86 (m, 1H), 2.77(dd, 1H, J = 6.7, 13.2 Hz), 2.89-2.92 (m, 2H), 2.99-3.11 (m, J)3H), 3.75-3.80 (m, 2H), 4.60 (d, 1H, J = 8.4 Hz), 6.68 (d, 2H, J = 8.3 Hz), 7.19–7.30 (m, 5H), 7.54 (d, 2H, J = 8.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 19.9, 20.2, 27.2, 28.2, 29.7, 35.4, 53.8, 54.6, 58.7, 72.8, 79.6, 114.3, 126.4, 128.4, 129.5, 137.9, 150.3, 156.0; HRMS-ESI (m/z) [M + Na]⁺ calcd for C₂₅H₃₇N₃O₅S₁ 514.2352, found 514.2349.

A solution of above amine (74 mg, 0.151 mmol) in a mixture of 30% trifluoroacetic acid in CH₂Cl₂ (10 mL) was stirred 23 °C for 40 min. After this period, the reaction mixture was concentrated under reduced pressure and the residue was redissolved in CH₂Cl₂ (10 mL). To this solution were added (3R,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furanyl succinimidyl carbonate (16) (45 mg, 0.17 mmol) and triethylamine (155 μ L, 1.51 mmol). The resulting mixture was stirred at 23 °C for 3 h. The reaction mixture was then concentratated under reduced pressure, and the residue was purified by column chromatography over silica gel (2% MeOH in CHCl₃ as the eluent) to provide inhibitor 2 (75 mg, 89%) as a white amorphous solid: mp 74 °C dec; $R_f = 0.63$ (10% MeOH in CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.81 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.6 Hz), 1.42 - 1.46 (M, 1H), 1.57 - 1.65 (m, J)1H), 1.79-1.85 (m, 1H), 2.75-2.81 (m, 2H), 2.87-2.98 (m, 3H), 3.05-3.16 (m, 2H), 3.64-3.71 (m, 2H), 3.82-3.88 (m, 3H), 3.92-3.96 (m, 1H), 4.97-5.01 (m, 2H), 5.63 (d, 1H, J = 5.14Hz), 6.67 (d, 2H, J = 8.6 Hz), 7.18–7.28 (m, 5H), 7.53 (d, 2H, J = 8.6 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 19.9, 20.2, 25.8, 27.3, 29.7, 35.7, 45.4, 53.7, 55.1, 58.9, 69.6, 70.8, 72.8, 73.4, 109.3, 114.1, 126.0, 126.5, 128.5, 129.4, 137.7, 150.8, 155.4; HRMS-ESI (m/z) [M + Na]⁺ calcd for C₂₇H₃₇N₃O₇S₁ 570.2250, found 570.2257.

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Supporting Information Available: ¹H NMR and ¹³C NMR spectra for compounds **2**, **3**, **6**–**9**, **13a**, **14**–**16**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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