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Synthesis of dioxane-based antiviral agents and evaluation of their biological activities as inhibitors of Sindbis virus replication

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Abstract

The crystal structure of the Sindbis virus capsid protein contains one or two solvent-derived dioxane molecules in the hydrophobic binding pocket. A bisdioxane antiviral agent was designed by linking the two dioxane molecules with a three-carbon chain having R,R connecting stereochemistry, and a stereospecific synthesis was performed. This resulted in an effective antiviral agent that inhibited Sindbis virus replication with an EC50 of 14μM. The synthesis proceeded through an intermediate (*R*)-2-hydroxymethyl-[1,4]dioxane, which unexpectedly proved to be a more effecting antiviral agent than the target compound, as evidenced by its EC50 of 3.4μM as an inhibitor of Sindbis virus replication. Both compounds were not cytotoxic in uninfected BHK cells at concentrations of 1 mM.

1. Introduction

The alphaviruses are a genus of approximately 27 arthropod-transmitted plus-strand RNA viruses found in the *Togaviridae* family.[1,2] The viruses found in this group are responsible for a wide range of disease and many of them are important human and animal pathogens.[3,4] Several examples of alphaviruses are Sindbis, Semliki Forest, and Venezuelan equine encephalitis viruses. Infection can result in fever, rash, arthralgia or arthritis, lassitude, headache, and myalgia. The prototypic alphavirus is Sindbis virus (*SINV*), which is transmitted to humans through mosquito bites. At the present time, there are no effective antiviral agents for treatment of alphavirus infections.

We recently reported a preliminary account of an attempt to obtain dioxane-based antiviral agents by covalently linking two solvent-derived dioxane molecules found in the crystal structure of a Sindbis virus capsid protein (SINV CP) fragment.[5] The present communication provides a detailed description of the outcome of that effort, including the synthesis and biological testing of twenty-four dioxane derivatives in addition to the originally reported four compounds. These additional compounds include the enantiomer and meso diastereomer of the initial target compound, as well as homologues of various linker chain lengths. The results obtained from the full set of compounds document the correctness of the linker length and absolute configuration indicated by the structure-based drug design approach reported in the preliminary communication.[5]

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Crystallographic evidence supports the hypothesis that the intermolecular bonding of residues 108 and 110 in the N-terminal arm of the SINV CP molecule to a hydrophobic pocket on an adjacent capsid protein molecule is involved in capsid assembly.[6] Furthermore, an apparent structural analogy between residues L108 and L110 in the N-terminal arm and residues Y400 and L402 in the membrane E2 glycoprotein spikes suggests that the bonding of these glycoprotein residues to the hydrophobic pocket of the capsid protein is involved in the budding of virus from the cell.[6] The proposed role of the capsid residues L108 and L110 in capsid assembly has been confirmed by mutational studies. Similarly, mutational studies of the E2 glycoprotein have confirmed that residues Y400 and L402 play critical roles in the budding process.[6,7] These results indicate that small molecules that could bind to the hydrophobic binding pocket of the alphaviruses might effectively inhibit the viral replication cycle by blocking capsid assembly as well as budding from the cell. A SINV nucleocapsid protein fragment 114–264 having an "empty" hydrophobic pocket has been crystallized, and the resulting X-ray structure displayed a hydrophobic pocket occupied by one or two dioxane molecules derived from the crystallization solvent.[8] The two dioxane molecules occupy the same space as the two leucine residues (L108 and L110) present when the hydrophobic pocket is occupied by the N-terminal arm of an adjacent protein molecule.

The crystallography results suggest that the linkage of two dioxane molecules by a hydrocarbon linker chain could result in a potential drug molecule that would simultaneously occupy both dioxane-binding sites and thus display increased affinity for the protein relative to dioxane itself. A series of compounds that were predicted to bind in the hydrophobic pocket of the alphavirus capsid protein were therefore designed and synthesized. These ligands are expected to block the interaction of the viral capsid protein with the N-terminal arm of an adjacent capsid protein molecule, which could inhibit capsid assembly. In addition, the occupation of the hydrophobic binding pocket could also be expected to block the binding of the viral capsid protein to the membrane-bound E2 glycoprotein spikes, thus inhibiting viral budding.

2. Results and Discussion

2.1 Design

The general approach described above requires connecting two dioxane molecules by a linker chain. The length of the linker chain and the stereochemistry of the attachment are variables that must be considered carefully for the strategy to be successful. Therefore, molecular modeling was performed using the structure of the mutant SINV capsid protein SCP(114–264) (1WYK) occupied by two dioxane molecules.[8] Using a 10 Å sphere surrounding the two dioxane molecules as the starting template, the two dioxane molecules were extracted, linked, and docked back into the empty pocket. The energy of the ligand was then minimized using Sybyl® 7.0 while the protein structure was frozen. The investigation of an array of bis-dioxane molecules containing linker chains of various lengths and stereochemistries led to the conclusion that a three-carbon linker would allow the two dioxane moieties to occupy approximately the same space as the two dioxanes in the starting crystal structure. This encouraged the selection of the bis-dioxane **8** (Scheme 2) as the initial target compound. The hypothetical model of the dioxane dimer **8** bound in the hydrophobic binding pocket of the Sindbis virus capsid protein is displayed in Figure 1.

2.2 Chemistry

Synthesis of the dioxane analogues began from key intermediates (*R*)-2-hydroxymethyl-[1,4] dioxane **[(*R*)-4]** and (*S*)-2-hydroxymethyl-[1,4]dioxane **[(*S*)-4]**, which were readily prepared by our previously reported asymmetric synthesis (Scheme 1).[5,9] Three-carbon linker chain compounds **8**–**12** were synthesized from dithiane intermediate **7**, prepared as outlined in Scheme 2. Hydrolysis[10,11] of dithiane **7** with methyl iodide and sodium carbonate in aqueous

acetonitrile afforded the ketone **9**, and reduction of the carbonyl functional group with LAH provided the alcohol **10**. The carbonyl compound **9** was also transformed into two oxime derivatives **11** and **12** by reacting with hydroxylamine or methoxylamine in methanol containing two equivalents of pyridine.

In addition to the previously reported compound **14**,[5] the four-carbon linker chain compound **16** was synthesized from intermediate **6** in order to experimentally confirm that the optimal linker chain length was indeed three carbon atoms long. As outlined in Scheme 3, deprotonation of intermediate **6** with *n*-butyllithium in a mixed solvent of THF and HMPA, followed by reaction of the anion with iodide **29 (**Scheme 6), provided the dithiane **15**. The desired product **16** was obtained through desulfurization[12] with Raney nickel in refluxing ethanol and subsequent hydrogenation of the intermediate alkene with Pd/C. The ketone **17** was synthesized by hydrolysis of the dithiane **15**, and lithium aluminum hydride reduction of the ketone afforded the diastereomeric mixture of alcohols **18**.

In order to confirm that the stereochemistry of linker attachment represented in the R,R bis-dioxane **8** is in fact ideal, the corresponding enantiomer **25** and the meso compound **23** were synthesized as portrayed in Schemes 4 and 5. A key intermediate, dithiane **20**, was prepared as shown in Scheme 4. Intermediate **(*S*)-4** was converted to 2-iodomethyl-[1,4]dioxane **19**[13, 14] with imidazole, triphenylphophine, and iodine in a mixed solvent of toluene and tetrahydrofuran at ambient temperature in 84% yield.[15] Displacement of iodide from intermediate **19**[13,14] with the lithiated anion derived from 1,3-dithiane afforded the product **20**, which was readily hydrolyzed to yield aldehyde **21** with excess of methyl iodide and sodium bicarbonate in acetonitrile and water at 40 °C.

By employing the same strategies used in the synthesis of dioxane **8**, the meso dioxane analogue **23** and the chiral dioxane analogue **25** were synthesized (Scheme 5). The dithiane intermediates **22** and **24** were prepared by the treatment of starting material **20** with *n*-butyllithium in a mixed solvent of THF and HMPA, followed by reaction of the anion with each iodide **5** or **19**. The final products **23** and **25** were obtained from each of dithiane **22** or **24** through desulfurization[12] with Raney Nickel in refluxing ethanol.

The alcohol **(*R*)-4** unexpectedly proved to be more potent than bis-dioxane **8** as an inhibitor of viral replication.[5] This result led us to synthesize the corresponding homologated alcohols **27** and **31 (**Scheme 6) and to compare their biological activities with **(*R*)-4** and **8**. The hydrolysis[10,11] of **6** with methyl iodide and sodium carbonate in a mixed solvent of acetonitrile-water provided the aldehyde **26**, and subsequent reduction with sodium borohydride in methanol at ambient temperature afforded the alcohol **27** in nearly quantitative yield in two steps. The enantiomer **28** was obtained by sodium borohydride reduction of **21**. The alcohol compound **27** was iodinated with iodine in the presence of imidazole and triphenylphophine in a mixed solvent of toluene and tetrahydrofuran at ambient temperature to afford **29**. Coupling of iodide **29** with lithiated anion of 1,3-dithiane yielded intermediate **30**. The dithiane intermediate **30** was hydrolyzed with excess of methyl iodide and sodium bicarbonate, and the intermediate aldehyde reduced in the presence of sodium borohydride to yield a three-carbon extended alcohol product **31**. The Swern oxidation[16] was employed for the synthesis of aldehyde **32**, which was treated with methylmagnesium bromide to provide a diastereomeric mixture of alcohols **33**.

In order to further investigate the effect of linker chain length on antiviral activity, the synthesis of two five-carbon linker chain compounds **36** and **37** was performed as outlined in Scheme 7. The alcohol starting material **31** was converted to iodide **34** with iodine, imidazole and triphenylphosphine. The anion of **6**, generated in situ by deprotonation with *n*-butyllithium in a mixed solvent of THF-HMPA at −78 °C, was treated with iodide **34** to afford the alkylated

product **35**. Raney nickel desulfurization of **35** eliminated the dithiane moiety to provide a five-carbon linker chain compound **36** in 84% yield. Hydrolysis of the dithiane fragment of **35** with methyl iodide, followed by treatment with aqueous acetonitrile, afforded the corresponding ketone **37** in 88% yield.

2.3 Biological Results and Discussion

Biological assays were focused on testing for inhibition of SINV production and for cytotoxicity in uninfected baby hamster kidney (BHK) cells. Virus production using SIN-IRES-Luc was used to monitor antiviral activity. SIN-IRES-Luc is Sindbis virus with a fire-fly luciferase gene inserted at the 3' end of the genome, which is expressed off of an Internal Ribosomal Entry Site (IRES). The infectivity of the virus could be assayed directly as a measure of the luciferase amounts produced in infected cells over a period of time.

A cell viability assay was performed initially in order to plot a cytotoxicity curve for the compounds. A standard XTT-based colorimetric assay was employed using the “Quick Cell Proliferation Kit” (BioVision, Inc.). This involved treating BHK cells with various concentrations of the compounds and then using an XTT-conjugated substrate that formed an orange precipitate on reaction with mitochondrial dehydrogenases to determine cell viability. Spectrophotometric readings were taken at 450 nm and the intensity of the color was proportional to the viability of the cells. The cytotoxic concentrations for each of the compounds were established by comparing the spectrophotometric readings for the treated and untreated cells. In the assay for inhibition of Sindbis virus production, BHK cells were grown to confluency in 96-well plates. BHK cells were infected with SIN-IRES-Luc virus at a multiplicity of infection (MOI) of less than 1. Media containing the compounds at concentrations less than cytotoxic concentrations was added onto the infected cells, and the cells were further incubated at 37 °C for 12 h. Cell extracts were taken and luciferase assays were performed on the extracts using the LmaxII 96-well plate luminometer (Molecular Devices).[17,18]

Our initial molecular modeling studies indicated that a chiral bis-dioxane derivative having a three-carbon linker chain with R,R connecting stereochemistry would be ideal for binding to the Sindbis virus capsid protein (Figure 1). The results provided in Table 1 show that, indeed, connecting two dioxane molecules with a three-carbon linker does in fact provide an inhibitor of virus replication with an EC50 value of 14μM. The corresponding bis-dioxanes **16** and **36** with four-carbon and five-carbon linkers proved to be much less active, with EC50s of 1500 and 1000μM, respectively. Moreover, the enantiomer of **8** (bis-dioxane **25**) and the corresponding meso compound **23** were both inactive, so the stereochemistry of the linker attachment is obviously also important. These results demonstrate the validity of the structure-based drug design approach used to conceptually derive the active compound **8** from two inactive dioxane molecules.

The relatively high activity of the starting alcohol **(*R*)-4** as an inhibitor of viral replication (EC50 3.4μM) was a welcome surprise and it encouraged the synthesis of the homologated alcohols **27** and **31**. The alcohol **27**, which is a one-carbon homologue of **(*R*)-4**, proved to have greatly reduced antiviral activity, with an EC50 of 1400μM, while the next higher homologue **31** was completely inactive. The methylated analog **33** of **(*R*)-4** displayed significantly reduced activity, inhibiting viral replication with an EC50 of 99μM.

The possible binding mode of **(*R*)-4** to the capsid protein was investigated by molecular modeling using the procedure described for **8**. This resulted in the model displayed in Figure 2. The hypothetical structure displayed in Figure 2 indicates that it would be possible for the primary hydroxyl groups of two molecules of **(R)-4** to hydrogen bond to the Lys135 side chain and the backbone carbonyl of Gly251. This model essentially maintains the orientations of the

two dioxane molecules found in the crystal structure of SINV CP. There are clearly other residues lining the binding pocket that would be capable of hydrogen bonding to different orientations of the ligand **(R)-4**, including Met132, Glu133, Met137, and Thr253. Two bound molecules of **(R)-4** could also theoretically hydrogen bond to each other.

The bis-dioxanes **9–12** constitute a set of compounds having linker chains of the same length and connecting stereochemistry as the most active bis-dioxane **8**. The ketone **9**, as well as the corresponding oxime **11** and methoxime **12**, were all inactive, while the alcohol **10** retained a low level of antiviral activity (EC50 670μM). The bis-dioxane system **8** evidently does not tolerate functionalization at the central carbon atom.

Several of the dithiane intermediates were also tested as inhibitors of Sindbis virus replication. These included the dithianes **15**, **20**, **22**, and **24.** Compounds **15** and **22** were inactive, while intermediate **20** displayed a low level of antiviral activity (EC50 1000μM). However, the dithiane derivative **22** was much more active (EC50 20μM) than the others.

In addition to being tested antiviral activity, all of the compounds in the series were examined for cytotoxicity in uninfected BHK cells. All of the compounds were not cytotoxic at concentrations of 1000μM (Table 1). Three of the compounds [**(*S*)-3**, **21**, and **(*S*)-4**] were examined at concentrations of 5000μM without any apparent evidence of cytotoxicity. The therapeutic index (EC50/CC50 ratio) of **8** was therefore greater than 71, while that of **(*R*)-4** was greater than 294.

3. Summary

In summary, prior crystallographic studies of the Sindbis virus capsid protein showed the presence of one or two solvent-derived dioxane molecules in the hydrophobic binding pocket.[8] This structure provided a template for design of the dioxane-based antiviral agent **8**. Computer graphics molecular modeling indicated that two solvent-derived dioxane molecules found the hydrophobic binding pocket during crystallography could theoretically be linked by a three-carbon chain having R,R connection stereochemistry without appreciable movement of the two dioxane rings. A stereospecific route to the synthesis was carried out, and the investigation of the bis-dioxane **8** revealed that it in fact was an inhibitor of Sindbis virus replication, with an EC50 of 14μM. Lengthening the linker chain, changing the stereochemistry of the linker chain connection, or functionalization of the linker chain all resulted in complete or substantial loss of antiviral potency. Unexpectedly, the synthetic intermediate **(*R*)-4** proved to be the most active compound in the series, having an EC50 of 3.4μM. This study has proven to be fruitful example of structure-based drug design culminating in effective dioxane-based antiviral agents against Sindbis virus, a prototype of the alphavirus family. The dioxane-based antiviral agents are novel, and they provide a template for further development of antiviral agents targeted against alphaviruses.

4. Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Except where noted, NMR spectra were obtained at 300 MHz (^{1}H) and 75 MHz (^{13}C) using $CDCl_3$ as solvent and the solvent peak as internal standard. Flash chromatography was performed with 230–400 mesh silica gel. TLC was carried out using Baker-flex silica gel IB2-F plates of 250μm thickness. Compounds were visualized with short wavelength UV light. Unless otherwise stated, chemicals and solvents were reagent grade and used as obtained from commercial sources without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl radical prior to use. Dichloromethane was freshly distilled from calcium hydride prior to use. All yields given refer to isolated yields of pure products.

4.1(*R*)-1-(2-Chloroethoxy)-3-chloropropan-2-ol [(*R*)-2]

Epoxide **(*R*)-1** (5.0 mL, 64 mmol) was slowly added to a stirred solution of 2-chloroethanol (12.86 mL, 191.8 mmol) and $BF_3{\cdot}Et_2O$ (0.45 mL, 3.2 mmol) at 45 °C. The reaction mixture was heated on an oil bath for 1.5 h at 45 °C. Diethyl ether (100 mL) was added to this solution. The organic layer was washed with water (1 x 80 mL), dried over magnesium sulfate, and concentrated to yield a light brown liquid **(*R*)-2** (11.07 g, quantitative): IR (film) 3430, 2961, 2911, 2874, 1627, 1431, 1299, 1129 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 4.04–3.59 (m, 9 H), 2.61 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 71.7, 71.4, 70.1, 45.7, 42.8; EIMS *m/z* (rel intensity) 138 (M^+ – HCl, 1), 136 (M^+ – HCl, 5), 95 ($CH_2OCH_2CH_2Cl^+$, 33), 93 ($CH_2OCH_2CH_2Cl^+$, 100); CIMS *m/z* (rel intensity) 175 (MH^+, 17), 173 (MH^+, 27), 157 ($MH^+ – H_2O$, 61), 155 ($MH^+ – H_2O$, 100). Anal. Calcd for $C_5H_{10}Cl_2O_2$: C, 34.71; H, 5.82; Cl, 40.98. Found: C, 34.59; H, 5.81; Cl, 40.92.

4.2 (*S*)-1-(2-Chloroethoxy)-3-chloropropan-2-ol [(*S*)-2]

The procedure for the preparation of **(*R*)-2** was used for this compound, starting from epoxide **(*S*)-1.** The product was obtained as a light brown liquid (21.2 g, 96%): IR (film) 3430, 2961, 2911, 2874, 1627, 1431, 1299, 1129 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 4.04–3.59 (m, 9 H), 2.61 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 71.7, 71.4, 70.1, 45.7, 42.8; EIMS *m/z* (rel intensity) 138 (M^+ – HCl, 2), 136 (M^+ – HCl, 6), 95 ($CH_2OCH_2CH_2Cl^+$, 34), 93 ($CH_2OCH_2CH_2Cl^+$, 100); CIMS *m/z* (rel intensity) 175 (MH^+, 15), 173 (MH^+, 23), 157 ($MH^+ – H_2O$, 61), 155 ($MH^+ – H_2O$, 100). Anal. Calcd for $C_5H_{10}Cl_2O_2$: C, 34.71; H, 5.82; Cl, 40.98. Found: C, 34.62; H, 5.80; Cl, 40.83.

4.3 (*R*)-3-(2-Chloroethoxy)-1,2-epoxypropane [(*R*)-3]

(*R*)-1-(2-Chloroethoxy)-3-chloropropan-2-ol [**(*R*)-2]** (11 g, 64 mmol) was added dropwise to a stirred solution of NaOH (6.36 g, 159 mmol) in water (7.60 mL) on an ice-bath. The ice-bath was immediately removed after addition of **(*R*)-2**. After stirring 2 h at an ambient temperature, diethyl ether (150 mL) and water (50 mL) were added. The organic layer was washed with water (1 x 50 mL), dried over sodium sulfate and concentrated to give a light brown liquid **(*R*)-3** (7.0 g, 81%): IR (film) 2961, 2917, 2874, 1431, 1299, 1124 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.83–3.39 (m, 6 H), 3.14 (m, 1 H), 2.79–2.59 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 71.8, 71.3, 50.7, 44.0, 42.7; EIMS *m/z* (rel intensity) 100 (M^+ – HCl, 9), 57 (100); CIMS *m/z* (rel intensity) 139 (MH^+, 5), 137 (MH^+, 15), 101 (MH^+ – HCl, 100). Anal. Calcd for $C_5H_9ClO_2$: C, 43.97; H, 6.64; Cl, 25.96. Found: C, 43.88; H, 6.62; Cl, 25.90.

4.4 (*S*)-3-(2-Chloroethoxy)-1,2-epoxypropane [(*S*)-3]

The procedure for the preparation of **(*R*)-3** was used for this compound. The product was obtained as a clear liquid (14 g, 84%): IR (film) 2961, 2917, 2874, 1431, 1299, 1125 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.83–3.39 (m, 6 H), 3.14 (m, 1 H), 2.79–2.59 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 71.8, 71.3, 50.7, 44.0, 42.7; EIMS *m/z* (rel intensity) 100 (M^+ – HCl, 12), 57 (100); CIMS *m/z* (rel intensity) 139 (MH^+, 4), 137 (MH^+, 16), 101 (MH^+ – HCl, 100). Anal. Calcd for $C_5H_9ClO_2$: C, 43.97; H, 6.64; Cl, 25.96. Found: C, 43.94; H, 6.63; Cl, 25.88.

4.5 (*S*)-2-Hydroxymethyl-[1,4]dioxane [(*S*)-4]

(*R*)-3-(2-Chloroethoxy)-1,2-epoxypropane [**(*R*)-3]** (5.5 g, 41 mmol) was added to a solution of NaOH (4.09 g, 102 mmol) in water (40 mL) at room temperature. The reaction mixture was heated on an oil bath for 2 h at 90 °C. The resulting solution was extracted overnight at 50 °C through a high density continuous extractor with dichloromethane (50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 2:1 to 3:1) to give a clear liquid **(*S*)-4** (1.74 g, 36%): IR (film) 3436, 2959, 2915, 2860, 1647, 1453, 1124, 1084, 1045 $cm^{-1;}$ ^1H NMR

($CDCl_3$) δ 3.85–3.41 (m, 9 H), 2.15 (brs, 1 H); ^{13}C NMR ($CDCl_3$) 75.5, 67.7, 66.2, 66.0, 61.9; $[\alpha]_D$ = +3.0 (c= 1, EtOH); EIMS *m/z* (rel intensity) 118 (M^+, 5), 87 ($M^+ - CH_2OH$, 100); CIMS *m/z* (rel intensity) 119 (MH^+, 79), 101 ($MH^+ - H_2O$, 100). Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.64; H, 8.50.

4.6 (*R*)-2-Hydroxymethyl-[1,4]dioxane [(*R*)-4]

The procedure for the preparation of **(*S*)-4** was used for this compound, starting from **(*S*)-3**. The product was obtained as a light yellow liquid (4.28 g, 36%): IR (film) 3436, 2959, 2915, 2859, 1645, 1453, 1124, 1084, 1045 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.85–3.41 (m, 9 H), 2.15 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 75.5, 67.7, 66.2, 66.0, 61.9; $[\alpha]^{20}_D$ = −3.0 (c = 1, EtOH); EIMS *m/z* (rel intensity) 118 (M^+, 5), 87 ($M^+ - CH_2OH$, 100); CIMS *m/z* (rel intensity) 119 (MH^+, 76), 101 ($MH^+ - H_2O$, 100). Anal. ($C_5H_{10}O_3$) C, H.

4.7 (*S*)-2-Iodomethyl-[1,4]dioxane (5)

Imidazole (0.24 g, 3.5 mmol), triphenylphosphine (0.47 g, 1.8 mmol), and iodine (0.45 g, 1.8 mmol) were successively added to a solution of alcohol **(*R*)-4** (0.2 g, 1.69 mmol) in toluene (10 mL). After stirring for 1 h at room temperature, THF (5 mL) was added and the mixture was allowed to stir 2 h. The resulting solution was quenched with saturated $Na_2S_2O_3$ solution (10 mL) and extracted with diethyl ether (3 x 20 mL). The extracts were washed with brine (1 x 30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was extracted with ether-hexane (3 mL/20 mL) to remove solid triphenylphosphine oxide. The extract was concentrated and purified by column chromatography (EtOAc-hexane = 1:6) to give a clear liquid **5** (0.36 g, 93%): IR (film) 2960, 2855, 1449, 1107, 913, 879 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.91–3.49 (m, 6 H), 3.28 (dd, *J* = 9.5 Hz, 9.5 Hz, 1 H), 3.05 (d, *J* = 6.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 74.1, 70.4, 66.6, 66.0, 2.7; EIMS *m/z* (rel intensity) 228 (M^+, 100), 101 ($M^+ - I$, 66); CIMS *m/z* (rel intensity) 229 (MH^+, 100). Anal. Calcd for $C_5H_9IO_2$: C, 26.34; H, 3.98; I, 55.65. Found: C, 26.27; H, 3.98; I, 55.67.

4.8 (*R*)-2-([1,3]Dithian-2-ylmethyl)-[1,4]dioxane (6)

A 2.4 M solution of *n*-BuLi (0.73 mL, 1.8 mmol) in hexane was added to a solution of 1,3-dithiane (0.25 g, 2.1 mmol) in THF (2.5 mL) and HMPA (0.5 mL) at −70 °C. The solution was allowed to stir for 1 h between −10 °C and −20 °C, and cooled to −70 °C. A solution of iodide **5** (0.16 g, 0.70 mmol) in THF (2.0 mL) was added via cannula. The reaction mixture was slowly warmed up to room temperature overnight, quenched with water (15 mL) and brine (10 mL), and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:7) to give a yellow solid **6** (0.15 g, 98%): mp 63.5–64.5 °C. IR (film) 2907, 2852, 1422, 1278, 1123 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 4.22 (m, 1 H), 3.91–3.55 (m, 6 H), 3.29 (t, *J* = 9.9 Hz, 1 H), 2.99–2.75 (m, 4 H), 2.19–1.57 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 71.5, 70.9, 66.6, 66.4, 42.7, 37.4, 30.4, 29.9, 25.8; EIMS *m/z* (rel intensity) 220 (M^+, 49), 119 ($M^+ - C_5H_9O_2$, 100); CIMS *m/z* (rel intensity) 221 (MH^+, 100). Anal. Calcd for $C_9H_{16}O_2S_2$: C, 49.06; H, 7.32; S, 29.10. Found: C, 49.21; H, 7.34; S, 29.21.

4.9 1,3-Bis{(*R*)-[1,4]dioxan-2-yl}-2-([1,3]dithian-2-yl)propane (7)

A 2.4 M solution of *n*-BuLi (0.22 mL, 0.52 mmol) in hexane was added to a solution of 1,3-dithianate **6** (0.12 g, 0.54 mmol) in THF (2.5 mL) and HMPA (0.5 mL) at −70 °C. The solution was allowed to stir for 1 h between −10 °C and −20 °C, and cooled to −70 °C. A solution of iodide **5** (0.10 g, 0.45 mmol) in THF (2.0 mL) was added *via* cannula. The reaction mixture was slowly warmed up to room temperature for 3 h, quenched with water (10 mL) and brine (10 mL), and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column

chromatography (EtOAc-hexane = 1:7) to give a light yellow oil **7** (0.11 g, 76%): IR (film) 2953, 2907, 2850, 1735, 1446, 1279, 1122, 1105 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.97–3.55 (m, 12 H), 3.32 (t, *J* = 10.5 Hz, 2 H), 2.89–2.65 (m, 4 H), 2.19–1.88 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 72.8, 71.2, 66.4, 66.1, 50.6, 42.1, 26.3 24.5; EIMS *m/z* (rel intensity) 320 (M^+, 5), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 321 (MH^+, 100). Anal. Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55; S, 20.01. Found: C, 52.61; H, 7.52; S, 19.99.

4.10 1,3-Bis{(*R*)-[1,4]dioxan-2-yl}propane (8)

A solution of **7** (80 mg, 0.25 mmol) in absolute ethanol (5.0 mL) was added to a suspension of Raney nickel (0.5 g, pore size *ca*. 50μm) in absolute ethanol (10 mL) at room temperature. The mixture was heated at reflux for 5 h, and the resulting solution was decanted. The decanted solution was concentrated and purified by column chromatography (EtOAc-hexane = 1:1 to only EtOAc) to give a clear liquid **8** (23.6 mg, 44%): IR (film) 2953, 2911, 2851, 1449, 1112 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.80–3.48 (m, 12 H), 3.26 (dd, *J* = 10.0 Hz, *J* = 10.0 Hz, 2 H), 1.54–1.26 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 75.3, 71.3, 66.8, 66.5, 31.6, 20.9; $[\alpha]_D^{23}$ = −0.2 (c = 1, EtOH); EIMS *m/z* (rel intensity) 216 (M^+, 14), 112 ($C_6H_8O_2^+$, 100); CIMS *m/z* (rel intensity) 217 (MH^+, 100). **).** Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.99; H, 9.30.

4.11 1,3-Bis{(*R*)-[1,4]dioxan-2-yl}-2-propanone (9)

Methyl iodide (0.14 mL, 2.2 mmol) and sodium bicarbonate (92 mg, 1.1 mmol) in water (4.0 mL) were added to a solution of the 1,3-dithiane **7** (70 mg, 0.22 mmol) in acetonitrile (4.0 mL) at room temperature. The reaction mixture was stirred 12 h at 40 °C and cooled to room temperature. The resulting solution was added water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (EtOAc-hexane = 3:2 to only EtOAc) to give a clear liquid **9** (40 mg, 80%): IR (film) 2959, 2906, 2854, 1718, 1124 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 4.06 (m, 2 H), 3.80–3.55 (m, 10 H), 3.29 (dd, *J* = 10.0 Hz, *J* = 10.0 Hz, 2 H), 2.63 (dd, *J* = 7.5 Hz, *J* = 7.5 Hz, 2 H), 2.41 (dd, *J* = 5.1 Hz, *J* = 5.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 205.4, 71.8, 71.0, 67.1, 66.7, 46.0; $[\alpha]_D^{23}$ = −0.1 (c = 1, EtOH); EIMS *m/z* (rel intensity) 230 (M^+, 10), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 231 (MH^+, 100). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.37; H, 7.90.

4.12 1,3-Bis{(*R*)-[1,4]dioxan-2-yl}propan-2-ol (10)

A solution of 1.0 M lithium aluminum hydride (0.22 mL, 0.22 mmol) in diethyl ether was added to a solution of the ketone **9** (51.1 mg, 0.222 mmol) in THF (3.0 mL) at room temperature. The reaction mixture was stirred 1 h at room temperature, and then quenched with water (5 mL). The solution was extracted with ethyl acetate (1 x 10 mL) and dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate and concentrated to give a white solid **10** (46.5 mg, 90%): mp 59.5–60 °C. IR (film) 3460, 2954, 2912, 2853, 1448, 1124 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 4.05 (m, 1 H), 3.85–3.52 (m, 12 H), 3.34–3.25 (m, 2 H), 1.54–1.39 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 76.2, 74.7, 72.3, 71.4, 70.9, 67.2, 66.7, 66.4, 66.3, 39.0, 38.4; EIMS *m/z* (rel intensity) 214 ($M^+ - H_2O$, 1), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 233 (MH^+, 100), 215 ($MH^+ - H_2O$, 61). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 55.75; H, 8.65.

4.13 1,3-Bis{(*R*)-[1,4]dioxan-2-yl}-2-oximinopropane (11)

Hydroxylamine hydrochloride (52.8 mg, 0.760 mmol) and pyridine (0.123 mL, 1.52 mmol) were added to a solution of the ketone **9** (35 mg, 0.15 mmol) in MeOH (3.0 mL) in a sealed tube. The reaction mixture was heated on an oil bath 40 h at 65 °C and cooled to room temperature. The methanol solvent was evaporated under reduced pressure, and the residue was added ethyl acetate (10 mL) and water (10 mL). The mixture was extracted with ethyl

acetate (3 x 10 mL). The organic layer was washed with water (20 mL), dried over sodium sulfate and concentrated to give the desired product **11** as a clear liquid (36.3 mg, 97%). IR (film) 3340, 2959, 2909, 2855, 1651, 1448, 1362, 1123 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 6.06 (brs, 1 H), 3.97–3.54 (m, 12 H), 3.32 (m, 2 H), 2.68–2.36 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 155.7, 73.0, 72.7, 71.0, 70.8, 66.8, 66.7, 66.3, 66.2, 37.1, 30.4; ESIMS *m/z* (relative intensity) 268 (MNa^+, 100), 246 (MH^+, 70). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.77; H, 7.83; N, 5.70.

4.14 1,3-Bis{(*R*)-[1,4]dioxane-2-yl}-2-(methyloximino)propane (12)

Methoxylamine hydrochloride (49.5 mg, 0.593 mmol) and pyridine (0.10 mL, 1.2 mmol) were added to a solution of the ketone **9** (27.3 mg, 0.119 mmol) in MeOH (3.0 mL) in a sealed tube. The reaction mixture was heated on an oil bath 40 h at 65 °C and cooled to room temperature. The methanol solvent was evaporated under reduced pressure, and ethyl acetate (10 mL) and water (10 mL) were added to the residue. The mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with water (20 mL), dried over sodium sulfate and concentrated to give the desired product **12** as a light yellow liquid (28.3 mg, 92%). IR (film) 2958, 2906, 2853, 1448, 1362, 1123 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.91–3.54 (m, 12 H), 3.87 (s, 3 H), 3.34–3.24 (m, 2 H), 2.54–2.24 (m, 4 H); ^{13}C NMR δ ($CDCl_3$) 154.9, 73.6, 73.3, 73.2, 71.4, 67.2, 66.8, 61.8, 37.6, 37.4, 31.2, 30.9; ESIMS *m/z* 282 (100, MNa^+). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.56; H, 8.18; N, 5.38.

4.15 (*R*)-2-(2-Phenethyl-[1,3]dithian-2-ylmethyl)-[1,4]dioxane (13)

A 2.4 M solution of *n*-BuLi (0.28 mL, 0.67 mmol) in hexane was added to a solution of 1,3-dithianate **6** (0.14 g, 0.64 mmol) in THF (2.5 mL) and HMPA (0.5 mL) at −70 °C. The solution was allowed to stir for 1 h between −10 °C and −20 °C, and cooled to −70 °C. A solution of (2-iodoethyl)benzene (0.10 mL, 0.69 mmol) in THF (2.0 mL) was added *via* cannula. The reaction mixture was slowly warmed up to room temperature for 3 h, quenched with water (10 mL) and brine (10 mL), and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:6) to provide as a mixture of the desired product **13** (0.14 g, 70%) and the starting material **6 (**30%) as a light yellow oil. After characterization of the mixture by ^1H NMR, ^{13}C NMR, and EI/CI mass spectral data, the crude product was used directly in the next reaction. ^1H NMR ($CDCl_3$) δ 7.34–7.18 (m, 5 H), 3.85–3.55 (m, 7 H), 2.97–2.70 (m, 6 H), 2.31–1.81 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.9, 128.4, 128.3, 125.8, 72.6, 71.2, 66.4, 66.2, 51.8, 41.1, 40.0, 30.8, 26.0, 25.1; EIMS *m/z* (rel intensity) 324 (M^+, 20), 91 ($C_7H_7^+$, 83), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 325 (MH^+, 100).

4.16 (*R*)-2-(4-Phenylbutyl)-[1,4]dioxane (14)

A solution of the mixture of 70% of **13** (0.14 g, 0.44 mmol) and 30% of **6** in absolute ethanol (5.0 mL) was added to a suspension of Raney nickel (0.5 g, pore size *ca*. 5μ) in absolute ethanol (10 mL) at room temperature. The mixture was heated at reflux for 15 h, and the resulting solution was filtered through a Celite layer. The filtrate was concentrated and diluted with dichloromethane (30 mL) and washed with water (1 x 30 mL). The organic layer was dried over sodium sulfate and concentrated under the reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:1 to only EtOAc) to afford a clear liquid **14** (70 mg, 71%): IR (film) 3026, 2934, 2853, 1604, 1496, 1453, 1125 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 7.57–7.40 (m, 5 H), 4.05–3.74 (m, 6 H), 3.52 (dd, *J* = 10.1 Hz, *J* = 10.1 Hz, 1 H), 2.88 (t, *J* = 7.7 Hz, 2 H), 1.96–1.55 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 142.5, 128.4, 128.3, 125.7, 75.3, 71.4, 66.8, 66.5, 35.8, 31.6, 31.5, 24.8; $[\alpha]_D^{23}$ = −1.4 (c = 1, EtOH); EIMS *m/z* (rel intensity) 220 (M^+, 3), 91 ($C_7H_7^+$, 100); CIMS *m/z* (rel intensity) 221 (MH^+, 100). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.60; H, 9.17.

4.17 1,4-Bis{(*R*)-[1,4]dioxan-2-yl}-2-([1,3]dithian-2-yl)butane (15)

A solution of 1.97 M *n*-BuLi (0.22 mL, 0.43 mmol) in hexane was added to a solution of **6** (0.090 g, 0.41 mmol) in THF (2.0 mL) and HMPA (0.3 mL) at −70 °C. The solution was allowed to stir for 10 min between −70 °C and −60 °C, and cooled to −70 °C. A solution of iodide **29** (0.09 g, 0.3718 mmol) in THF (1.0 mL) was added *via* cannula. The reaction mixture was slowly warmed up to room temperature for 2 h, quenched with water (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:3 to 1:2) to yield a light yellow oil **15** (0.12 g, 99%): IR (film) 2953, 2907, 2851, 1447, 1277, 1123 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.93–3.46 (m, 12 H), 2.36–3.24 (m, 2 H), 2.89–2.70 (m, 4 H), 2.28–1.53 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 75.4, 72.4, 71.2, 71.1, 66.7, 66.4, 66.2, 51.7, 40.5, 40.0, 34.3, 26.5, 26.0, 25.0; EIMS *m/z* (rel intensity) 334 (M^+, 45), 87 ($C_4H_7O_2^+$, 100). Anal. Calcd for $C_{15}H_{26}O_4S_2$: C, 53.86; H, 7.83; S, 19.17. Found: C, 53.84; H, 7.85; S 19.09.

4.18 1,4-Bis{(*R*)-[1,4]dioxan-2-yl}butane (16)

A solution of starting material **15** (53 mg, 0.16 mmol) in absolute ethanol (2.0 mL) was added to a suspension of Raney nickel (0.3 g, pore size ca. 50μm) in absolute ethanol (5 mL) at room temperature. The mixture was heated at reflux for 12 h, and the resulting solution was decanted to remove the nickel catalyst. The decanted solution was concentrated and purified by short-pass column chromatography (EtOAc-hexane = 1:3 to only EtOAc) to give an oily product. The oily product was dissolved in ethanol (2.0 mL), and this solution was added to a suspension of Pd/C (10%, 0.3 g) in ethanol (3.0 mL). The mixture was stirred 15 h under hydrogen, and the resulting solution was decanted to remove the palladium catalyst. The decanted solution was concentrated and purified by short-path column chromatography (EtOAc-hexane = 1:3 to only EtOAc) to give a white solid **16** (36 mg, 100%): mp 78.5–79.5 °C. IR (film) 2927, 2904, 2855, 1458, 1127 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.82–3.49 (m, 12 H), 3.35–3.23 (m, 2 H), 2.69–1.24 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 75.3, 71.3, 66.8, 66.5, 31.5, 25.1; EIMS *m/z* (rel intensity) 230 (M^+, 9), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 231 (MH^+, 59), 169 (MH^+ – 62, 100). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.53; H, 9.60.

4.19 1,4-Bis{(*R*)-[1,4]dioxan-2-yl}-2-butanone (17)

Methyl iodide (0.13 mL, 2.1 mmol) and sodium bicarbonate (89.8 mg, 1.07 mmol) in water (4.0 mL) were added to a solution of dithiane **15** (71.5 mg, 0.214 mmol) in acetonitrile (4.0 mL) at room temperature. The reaction mixture was stirred overnight at 40 °C and cooled to room temperature. The resulting solution was added to water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (EtOAc-hexane = 1:1 to EtOAc only) to give a white solid **17** (14.1 mg, 27%): mp 61–62 °C. IR (film) 2963, 2910, 2851, 1709, 1112 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 4.10–4.00 (m, 1 H), 3.79–3.47 (m, 11 H), 3.33–3.23 (m, 2 H), 2.70–2.48 (m, 2 H), 2.36 (dd, *J* = 5.0 Hz, *J* = 5.0 Hz, 1 H), 1.76–1.53 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.3, 74.4, 71.6, 71.1, 70.7, 66.7, 66.4, 66.3, 44.7, 39.0, 25.0; EIMS *m/z* (rel intensity) 244 (M^+, 4), 87 ($C_4H_7O_2$, 100); CIMS *m/z* (rel intensity) 245 (MH^+, 63), 183 (MH^+ – 62, 100). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.23; H, 8.23.

4.20 1,4-Bis{(*R*)-[1,4]dioxan-2-yl}butan-2-ol (18)

A solution of 1.0 M lithium aluminum hydride (0.13 mL, 0.13 mmol) in diethyl ether was added to a solution of the ketone starting material **17** (31.8 mg, 0.13 mmol) in THF (3.0 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature and then quenched with slow addition of water (10 mL). The solution was extracted with ethyl acetate (1 x 10 mL) and dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate

and concentrated to give a white solid **18** (28 mg, 87%) containing a 2:1 mixture of diastereomers. IR (film) 3509, 3446, 2966, 2939, 2916, 2859, 1458, 1443, 1122 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.88–3.50 (m, 13 H), 3.36–3.22 (m, 2 H), 1.65–1.37 (m, 6 H); ^{13}C NMR ($CDCl_3$), major diastereomer, δ 76.2, 75.2, 73.0, 71.3, 71.0, 70.5, 67.8, 66.8, 66.4, 37.8, 32.9, 27.2; EIMS *m/z* (rel intensity) 228 ($M^+ - H_2O$, 2), 145 ($M^+ - C_5H_9O_2$, 6), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 247 (MH^+, 32), 229 ($MH^+ - H_2O$, 100). Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.66; H, 8.96.

4.21 (*R*)-2-Iodomethyl-[1,4]dioxane (19)

Imidazole (0.59 g, 8.7 mmol), triphenylphosphine (1.17 g, 4.44 mmol), and iodine (1.13 g, 4.44 mmol) were successively added to a solution of alcohol **(*S*)-4** (0.50 g, 4.2 mmol) in toluene (10 mL). After stirring for 10 min at room temperature, THF (10 mL) was added, and the reaction mixture was allowed to stir 10 h. The resulting solution was quenched with saturated $Na_2S_2O_3$ solution (20 mL) and extracted with diethyl ether (3 x 20 mL). The extracts were washed with brine (1 x 30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was extracted with ether-hexane (3 mL/20 mL) to remove solid triphenylphosphine oxide. The extract was concentrated and purified by column chromatography (EtOAc-hexane = 1:6) to give a clear liquid **19** (0.81 g, 84%): IR (film) 2960, 2855, 1449, 1107, 913, 879 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.91–3.49 (m, 6 H), 3.28 (dd, *J* = 9.7 Hz, 9.7 Hz, 1 H), 3.05 (d, *J* = 6.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 74.2, 70.5, 66.7, 66.1, 2.7; EIMS *m/z* (rel intensity) 228 (M^+, 26), 127 (I^+, 100), 101 ($M^+ - I$, 48); CIMS *m/z* (rel intensity) 229 (MH^+, 49), 185 ($MH^+ - C_2H_4O$, 192), 101 ($MH^+ - HI$, 100). Anal. Calcd for $C_5H_9IO_2$: C, 26.34; H, 3.98; I, 55.65. Found: C, 26.42; H, 3.97; I, 55.49.

4.22 (*S*)-2-([1,3]Dithian-2-ylmethyl)-[1,4]dioxane (20)

A 1.95 M solution of *n*-BuLi (0.73 mL, 1.4 mmol) in hexane was added to a solution of 1,3-dithiane (0.2056 g, 1.710 mmol) in THF (2.0 mL) and HMPA (0.3 mL) at −78 °C. The solution was allowed to stir for 30 min between −78 °C and −65 °C, and cooled to −78 °C. A solution of iodide **19** (0.13 g, 0.57 mmol) in THF (1.0 mL) was added to the solution *via* cannula. The reaction mixture was slowly warmed up to room temperature overnight, quenched with water (5 mL) and brine (10 mL), and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:7) to give a yellow solid **20** (98 mg, 78%): mp 63–64 °C. IR (film) 2953, 2903, 2853, 1423, 1276, 1124 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 4.19 (qt, *J* = 4.5 Hz, 1 H), 3.91–3.55 (m, 6 H), 3.26 (dd, *J* = 9.9 Hz, *J* = 9.9 Hz, 1 H), 2.99–2.75 (m, 4 H), 2.19–1.57 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 71.5, 71.0, 66.7, 66.4, 42.3, 37.3, 30.4, 30.0, 25.8; EIMS *m/z* (rel intensity) 220 (M^+, 3), 119 ($C_4H_7S_2^+$, 100); CIMS *m/z* (rel intensity) 221 (MH^+, 92), 87 ($C_4H_7O_2^+$, 100). Anal. Calcd for $C_9H_{16}O_2S_2$: C, 49.06; H, 7.32; S, 29.10. Found: C, 48.92; H, 7.34; S, 29.18.

4.23 (*S*)-[1,4]Dioxan-2-yl-acetaldehyde (21)

Methyl iodide (1.13 mL, 18.2 mmol) and sodium bicarbonate (0.76 g, 9.1 mmol) in water (4.0 mL) were added to a solution of the 1,4-dioxanyl 1,3-dithiane **20** (0.40 g, 1.8 mmol) in acetonitrile (12.0 mL) at room temperature. The reaction mixture was stirred 15 h at 45 °C and cooled to room temperature. The resulting solution was to added water (15 mL) and the mixture extracted with ethyl acetate (3 x 15 mL) and dichloromethane (15 mL). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (EtOAc-hexane = 1:3 to 1:1) to give the desired product **21** as a clear liquid (0.18 g, 78%): IR (film) 2962, 2910, 2855, 2738, 1728, 1126, 1093 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1 H), 4.12 (m, 1 H), 3.57–3.72 (m, 5 H), 3.35 (dd, *J* = 10.0 Hz, *J* = 10.0 Hz, 1 H), 2.37–2.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 199.8, 70.5, 70.4, 66.7, 66.3, 45.4; EIMS *m/z* (rel

intensity) 130 (M^+, 3), 101 (M^+ – CHO, 45), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 131 (MH^+, 100). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.30; H, 7.72.

4.24 1,3-Bis{(*R*,*S*)-[1,4]dioxan-2-yl}-2-([1,3]dithian-2-yl)propane (22)

A 1.95 M solution of *n*-BuLi (0.33 mL, 0.65 mmol) in hexane was added to a solution of dithiane **20** (0.15 g, 0.68 mmol) in THF (2.5 mL) and HMPA (0.4 mL) at −78 °C. The solution was allowed to stir for 30 min between −78 °C and −65 °C, and cooled to −78 °C. A solution of iodide **5** (0.13 g, 0.59 mmol) in THF (1.5 mL) was added to the solution *via* cannula. The reaction mixture was slowly warmed up to room temperature over 3 h, quenched with water (5 mL) and brine (10 mL), and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:3) to give a light yellow solid **22** (0.16 g, 86%): mp 99.5–100.5 °C. IR (film) 2953, 2906, 2850, 1445, 1278, 1124, 1104 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.88–3.79 (m, 2 H), 3.78–3.49 (m, 10 H), 3.27 (t, *J* = 10.8 Hz, 2 H), 2.73–2.62 (m, 4 H), 2.06–1.83 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 72.6, 70.9, 66.4, 66.2, 50.6, 40.5, 26.3, 26.1, 24.8; EIMS *m/z* (rel intensity) 320 (M^+, 10), 219 ($M^+ – C_5H_9O_2$, 21), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 321 (MH^+, 25), 179 (100). Anal. Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55; S, 20.01. Found: C, 52.68; H, 7.53; S, 19.95.

4.25 1,3-Bis{(*R*,*S*)-[1,4]dioxan-2-yl}propane (23)

A solution of **22** (35.5 mg, 0.111 mmol) in absolute ethanol (2.0 mL) was added to a suspension of Raney nickel (0.25 g, pore size *ca*. 50μ) in absolute ethanol (3.0 mL) at room temperature. The mixture was heated at reflux for 20 h, and the resulting solution was decanted to remove the nickel catalyst. The decanted solution was concentrated and purified by column chromatography (EtOAc-hexane = 1:1) to give a clear liquid **23** (20.1 mg, 84%): IR (film) 2956, 2909, 2852, 1449, 1119 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.81–3.46 (m, 12 H), 3.35–3.22 (m, 2 H), 2.26–1.22 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 75.6, 71.3, 67.2, 66.9, 31.9, 21.0; EIMS *m/z* (rel intensity) 216 (M^+, 6), 112 ($C_6H_8O_2^+$, 100); CIMS *m/z* (rel intensity) 217 (MH^+, 100). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.00; H, 9.29.

4.26 1,3-Bis{(*S*)-[1,4]dioxan-2-yl}-2-([1,3]dithian-2-yl)propane (24)

A 1.95 M solution of *n*-BuLi (0.17 mL, 0.33 mmol) in hexane was added to a solution of dithiane **20** (76.2 mg, 0.346 mmol) in THF (2.0 mL) and HMPA (0.3 mL) at −78 °C. The solution was allowed to stir for 30 min between −78 °C and −65 °C, and cooled to −78 °C. A solution of iodide **19** (68.6 mg, 0.301 mmol) in THF (1.0 mL) was added to the above solution *via* cannula. The reaction mixture was slowly warmed up to room temperature over 3 h, quenched with water (5 mL) and brine (10 mL), and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:3) to give a light yellow oil **24** (82.4 mg, 86%): IR (film) 2953, 2906, 2851, 1446, 1278, 1123, 1105 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.89 (m, 2 H), 3.78–3.51 (m, 10 H), 3.29 (dd, *J* = 10.2 Hz, *J* = 10.2 Hz, 2 H), 2.87–2.69 (m, 4 H), 2.05–1.85 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 72.9, 71.3, 66.5, 66.2, 50.7, 42.1, 26.3, 24.6; EIMS *m/z* (rel intensity) 320 (M^+, 7), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 321 (MH^+, 9), 87 ($C_4H_7O_2^+$, 100). Anal. Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55; S, 20.01. Found: C, 52.36; H, 7.53; S, 19.96.

4.27 1,3-Bis{(*S*)-[1,4]dioxan-2-yl}propane (25)

A solution of **24** (37.6 mg, 0.118 mmol) in absolute ethanol (2.0 mL) was added to a suspension of Raney nickel (0.25 g, pore size *ca*. 50μm) in absolute ethanol (3.0 mL) at room temperature. The mixture was heated at reflux for 15 h, and the resulting solution was decanted to remove the nickel catalyst. The decanted solution was concentrated and purified by column

chromatography (EtOAc-hexane = 1:2 to 1:1) to give a clear liquid **25** (17 mg, 67%): IR (film) 2953, 2911, 2851, 1449, 1113 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.80–3.48 (m, 12 H), 3.24 (dd, *J* = 10.0 Hz, *J* = 10.0 Hz, 2 H), 1.54–1.20 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 75.3, 71.3, 66.8, 66.5, 31.6, 20.9; EIMS *m/z* (rel intensity) 216 (M^+, 10), 112 ($C_6H_8O_2^+$, 100); CIMS *m/z* (rel intensity) 217 (MH^+, 100). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.17; H, 9.30.

4.28 (*R*)-[1,4]Dioxan-2-yl-acetaldehyde (26)

Methyl iodide (1.41 mL, 22.7 mmol) and sodium bicarbonate (0.95 g, 11 mmol) in water (4.0 mL) were added to a solution of the 1,4-dioxanyl 1,3-dithiane **6** (0.50 g, 2.3 mmol) in acetonitrile (12.0 mL) at room temperature. The reaction mixture was stirred 12 h at 45 °C and cooled to room temperature. The resulting solution was to added water (15 mL) and the mixture extracted with ethyl acetate (3 x 15 mL) and dichloromethane (15 mL). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (EtOAc-hexane = 1:3 to 1:1) to give the desired product **26** as a clear liquid (0.29 g, 98%): IR (film) 2962, 2910, 2855, 2738, 1728, 1126, 1093 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1 H), 4.12 (m, 1 H), 3.57–3.72 (m, 5 H), 3.35 (dd, *J* = 10.0 Hz, *J* = 10.0 Hz, 1 H), 2.37–2.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 199.8, 70.5, 70.4, 66.7, 66.3, 45.4; EIMS *m/z* (rel intensity) 130 (M^+, 3), 101 (M^+ – CHO, 45), 86 ($C_4H_6O_2^+$, 100); CIMS *m/z* (rel intensity) 131 (MH^+, 100). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.30; H, 7.72.

4.29 (*R*)-2-[1,4]Dioxan-2-yl-ethanol (27)

Sodium borohydride (0.25 g, 6.7 mmol) was added to a solution of aldehyde **26** (0.29 g, 2.2 mmol) in methanol (8.0 mL) at room temperature. The reaction mixture was stirred for 30 min at ambient temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in water (10 mL) and extracted with dichloromethane (30 mL) using a high-density continuous extractor. The organic layer was dried over sodium sulfate and concentrated to give a clear oil **27** (0.29 g, quantitative): IR (film) 3413, 2958, 2857, 1655, 1450, 1124 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.83–3.57 (m, 8 H), 3.34 (dd, *J* = 10.2 Hz, *J* = 10.2 Hz, 1 H), 2.28 (s, 1 H), 1.72–1.54 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 75.2, 71.0, 66.8, 66.4, 60.4, 33.5; EIMS *m/z* (rel intensity) 132 (M^+, 16), 87 (M^+ – CH_2OH, 100); CIMS *m/z* (rel intensity) 133 (MH^+, 100), 115 (MH^+ – H_2O, 80). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.35; H, 9.18.

4.30 (*S*)-2-[1,4]Dioxan-2-yl-ethanol (28)

Sodium borohydride (6.1 mg, 0.16 mmol) was added to a solution of aldehyde **21** (7.0 mg, 0.054 mmol) in methanol (3.0 mL) at room temperature. The reaction mixture was stirred for 30 min at ambient conditions and the solvent was evaporated under reduced pressure. The residue was dissolved in water (10 mL) and extracted using a high-density continuous extractor with dichloromethane (30 mL). The organic layer was dried over sodium sulfate and concentrated to give a clear oil **28** (7.1 mg, quantitative): IR (film) 3413, 2958, 2857, 1655, 1450, 1124 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.83–3.57 (m, 8 H), 3.34 (dd, *J* = 10.2 Hz, *J* = 10.2 Hz, 1 H), 2.28 (s, 1 H), 1.72–1.54 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 75.2, 71.0, 66.8, 66.4, 60.4, 33.5; EIMS *m/z* (rel intensity) 132 (M^+, 16), 87 (M^+ – CH_2OH, 100); CIMS *m/z* (rel intensity) 133 (MH^+, 100), 115 (MH^+ – H_2O, 80). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.45; H, 9.17.

4.31 (*R*)-2-(2-Iodoethyl)-[1,4]dioxane (29)

Imidazole (0.20 g, 2.9 mmol), triphenylphosphine (0.40 g, 1.5 mmol), and iodine (0.38 g, 1.5 mmol) were added to a solution of alcohol **27** (0.19 g, 1.4 mmol) in toluene (5 mL). After stirring for 10 min at room temperature, THF (5 mL) was added and the mixture allowed to stir 12 h. The resulting solution was quenched with a saturated $Na_2S_2O_3$ solution (10 mL) and

extracted with diethyl ether (3 x 20 mL). The extracts were washed with brine (1 x 30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was extracted with ether-hexane (1 mL:10 mL) to remove solid triphenylphosphine oxide. The extract was concentrated and purified by column chromatography (EtOAc-hexane = 1:5) to give a clear liquid **29** (0.29 g, 84%): IR (film) 2957, 2853, 1446, 1120, 931, 968 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.80–3.56 (m, 6 H), 3.36–3.22 (m, 3 H), 1.98–1.89 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 74.9, 70.4, 66.7, 66.5, 35.3, 1.1; EIMS *m/z* (rel intensity) 242 (M^+, 11), 115 (M^+ – I, 46), 87 (M^+ – CH_2OH, 100); CIMS *m/z* (rel intensity) 243 (MH^+, 72), 199 ($MH^+ – C_2H_4O$, 100). Anal. Calcd for $C_6H_{11}IO_2$: C, 29.77; H, 4.58; I, 54.53. Found: C, 29.68; H, 4.59; I, 54.29.

4.32 (*R*)-2-(2-[1,3]Dithian-2-yl-ethyl}-[1,4]dioxane (30)

A 1.95 M solution of *n*-BuLi (0.26 mL, 0.52 mmol) in hexane was added to a solution of 1,3-dithiane (74.5 mg, 0.620 mmol) in THF (3.5 mL) and HMPA (0.5 mL) at −78 °C. The solution was allowed to stir for 30 min between −78 °C and −60 °C, and cooled to −78 °C. A solution of iodide **29** (50 mg, 0.21 mmol) in THF (1.5 mL) was added to the above solution *via* cannula. The reaction mixture was slowly warmed up to room temperature over 5 h, quenched with water (5 mL) and brine (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:6) to give a yellow solid **30** (47.5 mg, 98%): mp 90–91 °C. IR (film) 2950, 2902, 2851, 1448, 1422, 1276, 1125 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 4.04 (t, *J* = 6.9 Hz, 1 H), 3.80–3.55 (m, 6 H), 3.29 (dd, *J* = 9.9 Hz, *J* = 9.9 Hz, 1 H), 2.89–2.84 (m, 4 H), 2.18–1.1.74 (m, 4 H), 1.64–1.54 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 74.8, 71.1, 66.7, 66.5, 47.3, 31.0, 30.3, 28.5, 25.9; EIMS *m/z* (rel intensity) 234 (M^+, 33), 132 ($M^+ – C_5H_{10}O_2$, 100), 119 ($M^+ – C_6H_{11}O_2$, 83); CIMS *m/z* (rel intensity) 235 (MH^+, 100). Anal. Calcd for $C_{10}H_{18}O_2S_2$: C, 51.24; H, 7.71; S, 27.36. Found: C, 51.44; H, 7.71; S, 27.38.

4.33 (*R*)-3-([1,4]Dioxan-2-yl)propan-1-ol (31)

Methyl iodide (0.69 mL, 11.04 mmol) and sodium bicarbonate (0.46 g, 5.52 mmol) in water (10.0 mL) were added to a solution of the 1,3-dithiane **30** (0.26 g, 1.10 mmol) in acetonitrile (8.0 mL) at room temperature. The reaction mixture was stirred 12 h at 40 °C and cooled to room temperature. Water (10 mL) was added to the resulting solution and the mixture was extracted with ethyl acetate (2 x 10 mL) and dichloromethane (2 x 10 mL). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel flash chromatography (EtOAc-hexane = 3:1 to 1:1) to give an aldehyde intermediate as a clear liquid (0.13 g, 84%). The aldehyde was immediately used in the next step. Sodium borohydride (0.11 g, 2.79 mmol) was added to a solution of aldehyde (0.13 g, 0.93 mmol) in methanol (6.0 mL) at room temperature. The reaction mixture was stirred for 1 h at ambient condition and the solvent was evaporated under reduced pressure. The residue was dissolved in water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate and concentrated to give a clear liquid **31** (0.12 g, 85%): IR (film) 3413, 2953, 2918, 2854, 1652, 1449, 1125 $cm^{-1;}$ ^1H NMR ($CDCl_3$) δ 3.81–3.51 (m, 8 H), 3.27 (dd, *J* = 10.1 Hz, *J* = 10.1 Hz, 1 H), 1.98 (brs, 1 H), 1.71–1.62 (m, 2 H), 1.52–1.39 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 75.5, 71.2, 66.8, 66.4, 62.7, 28.8, 28.4; EIMS *m/z* (rel intensity), 146 (M^+, 1), 128 ($M^+ – H_2O$, 6), 87 ($C_4H_7O_2^+$, 72), 59 [$(CH_2)_3OH^+$, 100]; CIMS *m/z* (rel intensity) 147 (MH^+, 22), 129 ($MH^+ – H_2O$, 100). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.64; H, 9.62.

4.44 (*R*)-[1,4]Dioxane-2-carbaldehyde (32)

A solution of 2.0 M oxalyl chloride (1.46 mL, 2.92 mmol) in dichloromethane was diluted in dry dichloromethane (6.0 mL). Dimethyl sulfoxide (0.28 mL, 3.9 mmol) was added dropwise to this solution at −78 °C. After 10 min, a solution of dioxane-alcohol starting material ***(S)*-4**

(0.23 g, 2.0 mmol) in dichloromethane (4.0 mL) was added dropwise over 5 min at −78 °C, followed by addition of triethylamine (1.36 mL, 9.74 mmol). The reaction mixture was slowly warmed up to room temperature over 5 h and quenched with water (10 mL). The resulting solution was extracted with dichloromethane (3 x 10 mL), and the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc-hexane = 1:1 to 2:1) to give a clear liquid **32** (79.3 mg, 35%): IR (film) 2960, 2859, 1736, 1118 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 9.66 (s, 1 H), 4.12–3.37 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 200.0, 78.9, 74.1, 71.3, 68.2; EIMS *m/z* (rel intensity) 116 (M^+, 5), 87 (M^+ – CHO, 100); CIMS *m/z* (rel intensity) 117 (MH^+, 73), 99 (MH^+ – H_2O, 34) 87 (MH^+ – CHOH, 100). Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.63; H, 6.93.

4.45 1-{(*R*)-[1,4]Dioxane-2-yl}ethan-1-ol (33)

A solution of 3.0 M methylmagnesium bromide (0.26 mL, 0.78 mmol) in diethyl ether was added to a solution of the aldehyde **32** (60 mg, 0.52 mmol) in THF (3.0 mL) at room temperature. The reaction mixture was stirred for 2 h at room temperature, quenched with water (10 mL), and a solution of 4.0 N HCl (5 mL) was added. The solution was extracted with ethyl acetate (10 mL) and dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (EtOAc-hexane = 1:1 to 2:1) to give a clear liquid **33** (28.1 mg, 41%): IR (film) 3458, 2964, 2913, 2858, 1450, 1118 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.87–3.35 (m, 8 H), 2.07 (brs, 1 H), 1.13 (dd, *J* = 6.6 Hz, *J* =6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$), major diastereomer, δ 74.6, 71.9, 68.8, 68.3, 66.9, 18.7; EIMS *m/z* (rel intensity) 132 (M^+, 1), 87 ($C_4H_7O_2^+$, 100), 45 (CH_3CHOH^+, 100); CIMS *m/z* (rel intensity) 133 (MH^+, 3), 115 (MH^+ – H_2O, 100). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.63; H, 9.17.

4.46 (*R*)-2-(3-Iodopropyl)-[1,4]dioxane (34)

Imidazole (0.11 g, 1.6 mmol), triphenylphosphine (0.22 g, 0.83 mmol), and iodine (0.21 g, 0.83 mmol) were added to a solution of alcohol **31** (0.12 g, 0.79 mmol) in toluene (5 mL). After stirring for 10 min at room temperature, THF (5 mL) was added and the mixture allowed to stir 15 h. The resulting solution was quenched with saturated $Na_2S_2O_3$ solution (10 mL) and extracted with diethyl ether (3 x 20 mL). The extracts were washed with brine (1 x 30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was extracted with ether-hexane (1 mL:10 mL) to remove solid triphenylphosphine oxide. The extract was concentrated and purified by silica gel flash chromatography (EtOAc-hexane = 1:5) to give a clear liquid **34** (0.16 g, 77%): IR (film) 2955, 2909, 2851, 1447, 1121 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.76–3.49 (m, 6 H), 3.29–3.16 (m, 3 H), 2.04–1.78 (m, 2 H), 1.50–1.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 74.4, 71.2, 66.8, 66.5, 32.3, 29.1, 6.68; EIMS *m/z* (rel intensity) 256 (M^+, 0.2), 129 (M^+ – I, 100); CIMS *m/z* (rel intensity) 257 (MH^+, 17), 129 (MH^+ – HI, 100). Anal. Calcd for $C_7H_{13}IO_2$: C, 32.83; H, 5.12; I, 49.56. Found: C, 32.90; H, 5.14; I, 49.46.

4.47 1,5-Bis{(*R*)-[1,4]dioxan-2-yl}-2-{[1,3]dithian-2-yl}pentane (35)

A 1.60 M solution of *n*-BuLi in hexane (0.44 mL, 0.71 mmol) was added to a solution of dithiane (0.17 g, 0.77 mmol) in THF (3.0 mL) and HMPA (0.5 mL) at −78 °C. The solution was allowed to stir for 30 min between −78 °C and −40 °C, and cooled to −78 °C. A solution of iodide **34** (0.14 g, 0.55 mmol) in THF (2.0 mL) was added to the above solution *via* cannula. The reaction mixture was slowly warmed up to room temperature over 3 h, quenched with water (15 mL) and brine (10 mL), and extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc-hexane = 1:3 to 1:2) to give a light yellow oil **35** (92.1 mg, 48%): IR (film) 2952, 2908, 2851, 1447, 1277, 1123 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.90–3.79 (m, 1 H), 3.79–3.49 (m, 10 H), 3.32–3.20 (m, 2 H), 2.83–2.70 (m, 4 H),

2.03–1.80 (m, 6 H), 1.22–1.79 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 75.1, 72.9, 71.3, 66.9, 66.6, 66.3, 52.0, 40.1, 39.1, 31.7, 26.2, 25.2, 19.9; EIMS *m/z* (rel intensity) 348 (M^+, 72), 219 (M^+ – $C_7H_{13}O_2$, 56), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 349 (MH^+, 100). Anal. Calcd for $C_{16}H_{28}O_4S_2$: C, 55.14; H, 8.10; S, 18.40. Found: C, 55.22; H, 8.11; S, 18.35.

4.48 1,5-Bis{(*R*)-[1,4]dioxan-2-yl}pentane (36)

A solution of dioxanedithiane starting material **35** (55 mg, 0.16 mmol) in absolute ethanol (3.0 mL) was added to a suspension of Raney nickel (0.3 g, pore size *ca*. 50μm) in absolute ethanol (3 mL) at room temperature. The mixture was heated at reflux for 15 h, and the resulting solution was decanted to remove the nickel catalyst. The decanted solution was concentrated and purified by short-pass column chromatography (EtOAc-hexane = 1:3 to only EtOAc) to give a clear liquid **36** (32.4 mg, 84%): IR (film) 2933, 2853, 1449, 1115 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 3.77–3.64 (m, 8 H), 3.51–3.45 (m, 4 H), 3.23 (dd, *J* = 10.0 Hz, *J* = 10.0 Hz, 2 H), 1.48–1.21 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 75.3, 71.4, 66.8, 66.5, 31.6, 29.6 24.9; $[\alpha]^{22}_D$ = +2.1 (c = 0.574, $CHCl_3$); EIMS *m/z* (rel intensity) 244 (M^+, 4), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 245 (MH^+, 100). Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 64.01; H, 9.91.

4.49 1,5-Bis{(*R*)-[1,4]dioxan-2-yl}pentan-2-one (37)

Methyl iodide (71μL, 1.2 mmol) and sodium bicarbonate (48.2 mg, 0.57 mmol) in water (5.0 mL) were added to a solution of dithiane **35** (40 mg, 0.11 mmol) in acetonitrile (5.0 mL) at room temperature. The reaction mixture was stirred 12 h at 40 °C and cooled to room temperature. The resulting solution was added to water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (EtOAc-hexane = 1:1 to only EtOAc) to give a white solid **37** (26 mg, 88%): mp 47–47.5 °C. IR (film) 2936, 2885, 2855, 1701, 1115 $cm^{-1;}$ ^{1}H NMR ($CDCl_3$) δ 4.06–3.96 (m, 1 H), 3.76–3.44 (m, 11 H), 3.29–3.18 (m, 2 H), 2.55 (dd, *J* = 7.6 Hz, *J* = 7.6 Hz, 1 H), 2.45 (t, *J* = 7.2 Hz, 2 H), 2.30 (dd, *J* = 5.1 Hz, *J* = 5.1 Hz, 1 H), 1.77–1.52 (m, 2 H), 1.42–1.22 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 207.5, 75.1, 71.6, 71.2, 70.7, 66.7, 66.5, 66.3, 44.6, 43.4, 30.8, 19.1; $[\alpha]_D^{22}$ = +0.3 (c = 0.268, $CHCl_3$); EIMS *m/z* (rel intensity) 258 (M^+, 4), 87 ($C_4H_7O_2^+$, 100); CIMS *m/z* (rel intensity) 259 (MH^+, 27), 197 (MH^+ – 62, 89), 135 (MH^+ – 124, 100). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.37; H, 8.55.

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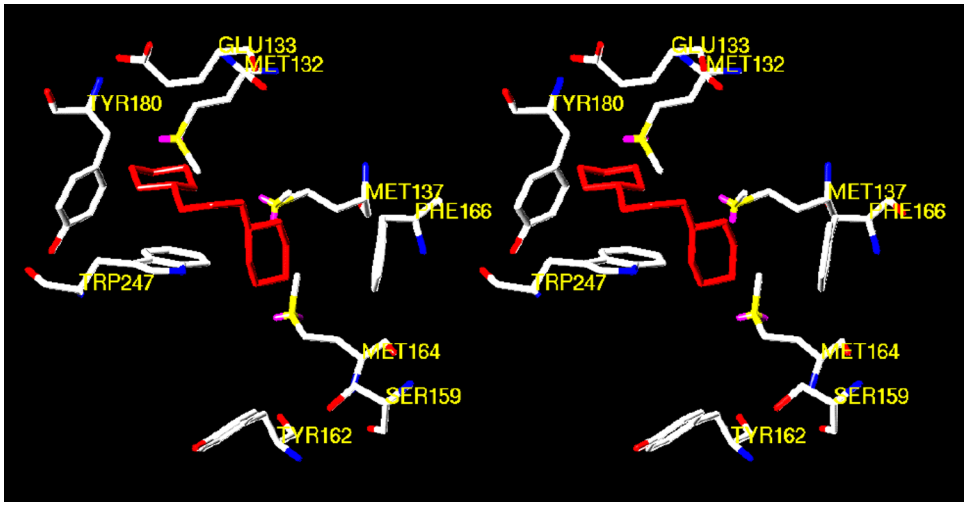


Figure 1.
Molecular model on the binding of the dioxane dimer **8** in the hydrophobic binding pocket of the Sindbis virus capsid protein. The figure is programmed for wall-eyed (relaxed) viewing.

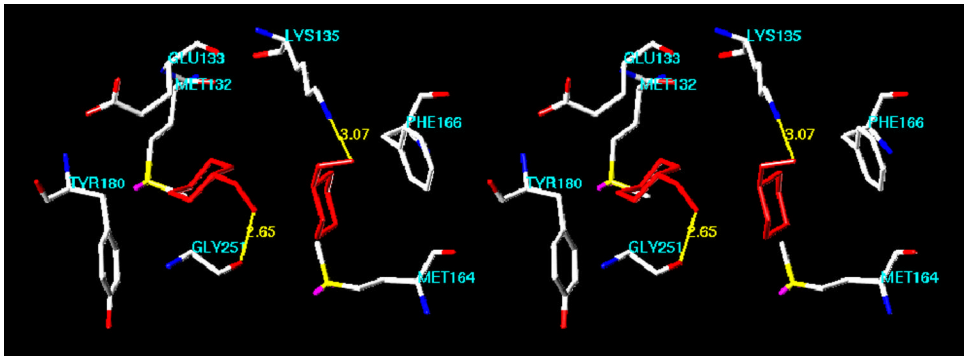
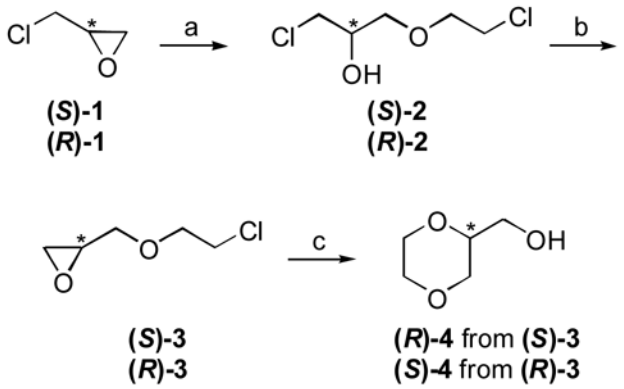
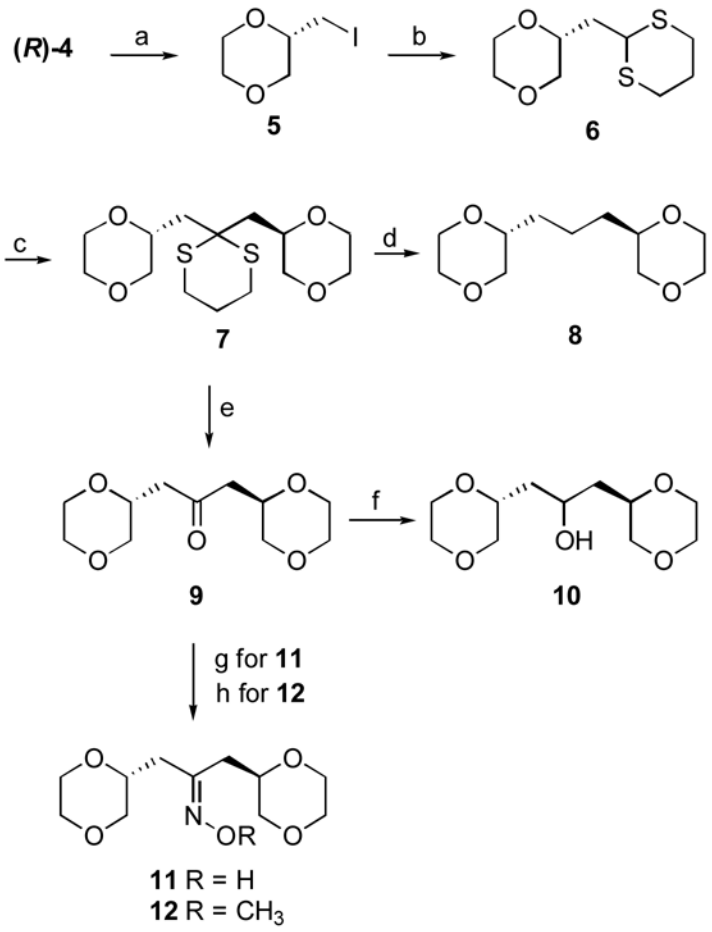


Figure 2.
Molecular model of the binding of the dioxane derivative **(R)-4** in the hydrophobic binding pocket of Sindbis virus capsid protein. The figure is programmed for wall-eyed (relaxed) viewing.



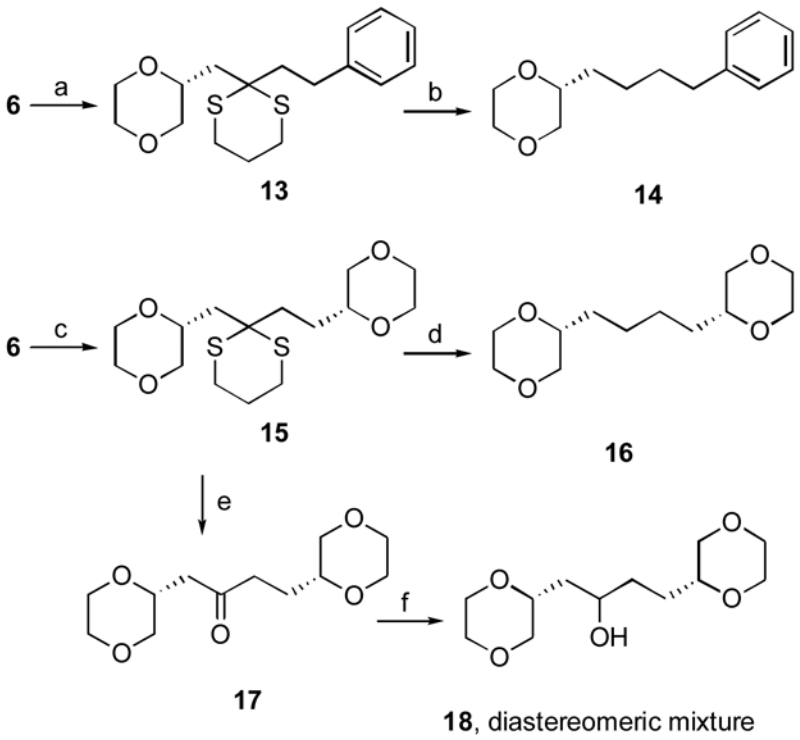
Scheme 1.

Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, 2-chloroethanol, 45 °C, 1.5 h; (b) NaOH, H_2O, rt, 2 h; (c) NaOH, H_2O, 90 °C, 2 h.



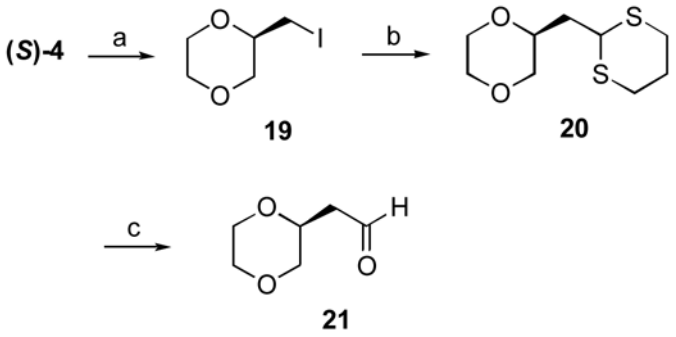
Scheme 2.

Reagents and conditions: (a) imidazole, PPh_3, I_2, toluene-THF, rt, 3 h; (b) 1,3-dithiane, *n*-BuLi, THF-HMPA, −70 °C to rt; (c) *n*-BuLi, **5**, THF-HMPA, −70 °C to rt; (d) Raney Ni, abs·EtOH, reflux, 5 h; (e) MeI, $NaHCO_3$, CH_3CN-H_2O, 40 °C, 12 h; (f) $LiAlH_4$, THF, rt, 1 h; (g) H_2NOH·HCl, pyridine, MeOH, 65 °C, 40 h, sealed tube; (h) H_2NOMe·HCl, pyridine, MeOH, 65 °C, 40 h, sealed tube.



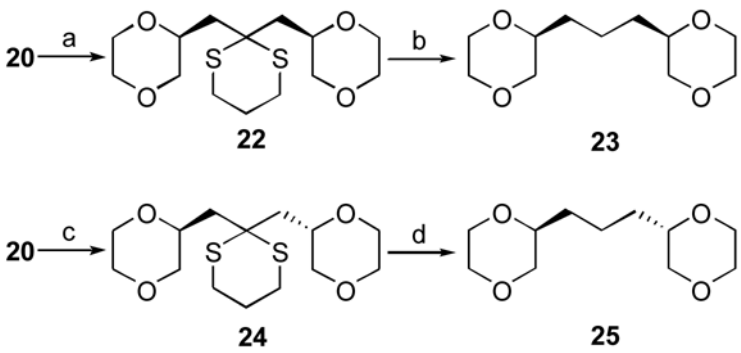
Scheme 3.

Reagents and conditions: (a) *n*-BuLi, (2-iodoethyl)benzene, THF-HMPA, −70 °C to rt; (b) Raney Ni, abs·EtOH, reflux, 15 h; (c) *n*-BuLi, **29**, THF-HMPA, −70 °C to rt; (d) i) Raney Ni, EtOH, reflux, 12 h, ii) 10% Pd/C, H_2, EtOH, rt, 15 h; (e) MeI, $NaHCO_3$, CH_3CN-H_2O, 40 °C, 15 h; (f) $LiAlH_4$, THF, rt, 1 h.



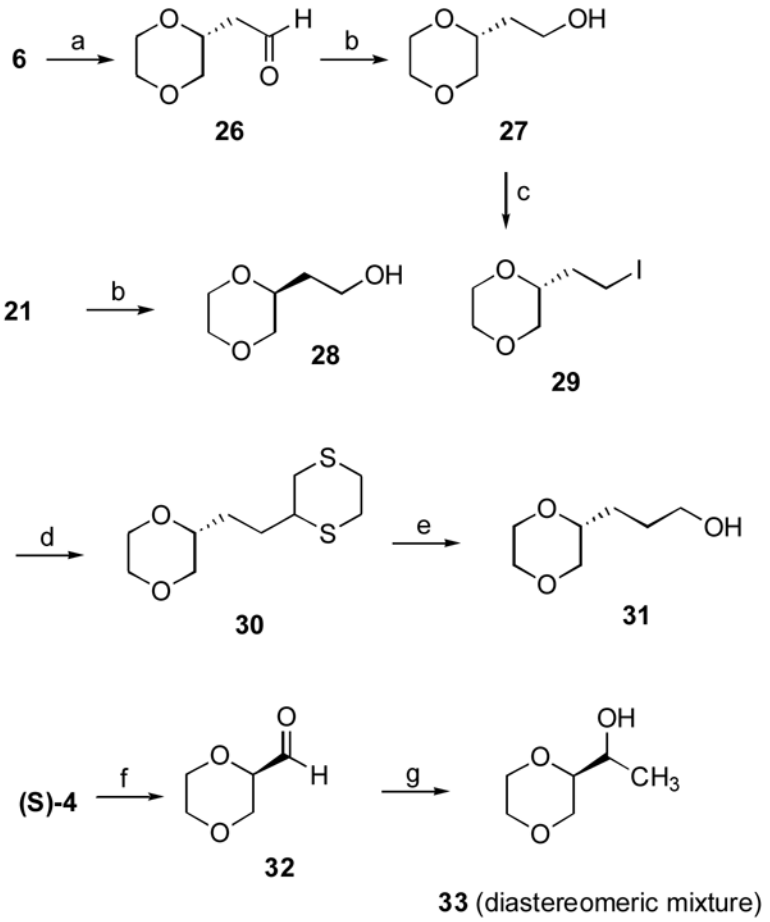
Scheme 4.

Reagents and conditions: (a) imidazole, PPh_3, I_2, toluene-THF, rt, 10 h; (b) 1,3-dithiane, *n*-BuLi, THF-HMPA, −78 °C to rt; (c) MeI, $NaHCO_3$, CH_3CN-H_2O, 40 °C, 15 h.



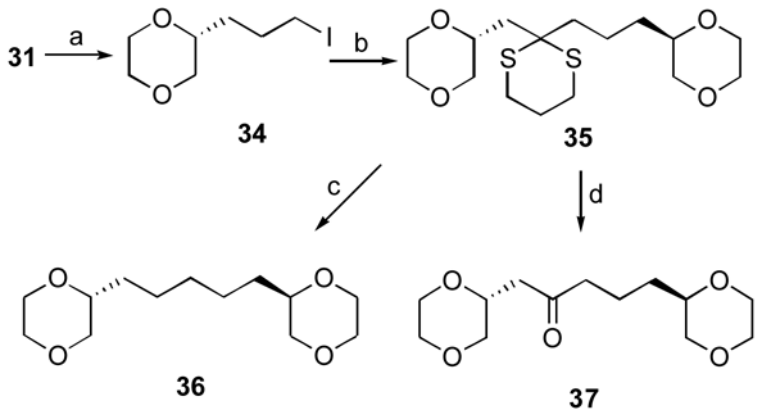
Schcme 5.

Reagents and conditions: (a) *n*-BuLi, **5**, THF-HMPA, −78 °C to rt; (b) Raney Ni, abs·EtOH, reflux, 20 h; (c) *n*-BuLi, **19**, THF-HMPA, −78 °C to rt; (d) Raney Ni, abs. EtOH, reflux, 15 h.



Scheme 6.

Reagents and conditions: (a) MeI, $NaHCO_3$, CH_3CN-H_2O, 40 °C, 12 h; (b) $NaBH_4$, MeOH, rt, 0.5 h; (c) imidazole, PPh_3, I_2, toluene-THF, rt, 12 h; (d) 1,3-dithiane, *n*-BuLi, THF-HMPA, −78 °C to rt; (e) i) MeI, $NaHCO_3$, CH_3CN-H_2O, 40 °C, 12 h, ii) $NaBH_4$, MeOH, rt, 1 h; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 5 h; (g) MeMgBr, THF, rt, 2 h.



Scheme 7.

Reagents and conditions: (a) imidazole, PPh_3, I_2, toluene-THF, rt, 15 h; (b) **6**, *n*-BuLi, THF-HMPA, −78 °C to rt; (c) Raney Ni, EtOH, 80 °C, 15 h; (d) MeI, $NaHCO_3$, CH_3CN-H_2O, 40 °C, 12 h.

Table 1

Antiviral Activities and Cytotoxicities of Dioxane Derivatives.

Compound	EC50 (M)[a]	CC50 (M)[b]
(*R*)-3	$1.0 \pm 0.90 \times 10^{-3}$	$>1 \times 10^{-3}$
(*S*)-3	$1.0 \pm 0.28 \times 10^{-3}$	$>5 \times 10^{-3}$
(*R*)-4	$3.4 \pm 0.45 \times 10^{-6}$	$>1 \times 10^{-3}$
(S)-4	$1.5 \pm 0.32 \times 10^{-3}$	$>5 \times 10^{-3}$
8	$1.4 \pm 0.25 \times 10^{-5}$	$>1 \times 10^{-3}$
9	NA[c]	$>1 \times 10^{-3}$
10	$6.7 \pm 0.23 \times 10^{-4}$	$>1 \times 10^{-3}$
11	NA	$>1 \times 10^{-3}$
12	NA	$>1 \times 10^{-3}$
14	NA	$>1 \times 10^{-3}$
15	NA	$>1 \times 10^{-3}$
16	$1.5 \pm 0.17 \times 10^{-3}$	$>1 \times 10^{-3}$
17	NA	$>1 \times 10^{-3}$
18	NA	$>1 \times 10^{-3}$
20	$1.0 \pm 0.43 \times 10^{-3}$	$>1 \times 10^{-3}$
21	$4.6 \pm 0.51 \times 10^{-4}$	$>5 \times 10^{-3}$
22	$2.9 \pm 0.36 \times 10^{-5}$	$>1 \times 10^{-3}$
23	NA	$>1 \times 10^{-3}$
24	NA	$>1 \times 10^{-3}$
25	NA	$>1 \times 10^{-3}$
27	$1.4 \pm 0.15 \times 10^{-3}$	$>1 \times 10^{-3}$
28	NA	$>1 \times 10^{-3}$
29	$2.5 \pm 0.19 \times 10^{-4}$	$>1 \times 10^{-3}$
30	NA	$>1 \times 10^{-3}$
31	NA	$>1 \times 10^{-3}$
33	$9.9 \pm 0.14 \times 10^{-5}$	$\sim 1 \times 10^{-3}$
36	$1.5 \pm 0.22 \times 10^{-3}$	$>1 \times 10^{-3}$
37	NA	
Chlorpromazine	$8.2 \pm 0.16 \times 10^{-6}$	1×10^{-4}
Verapamil	$1.3 \pm 0.17 \times 10^{-3}$	$>1 \times 10^{-3}$

[a] The EC50 is the concentration of the compound resulting in a 50% reduction in virus production.

[b] The CC50 is the concentration of the compound causing a 50% growth inhibition of uninfected BHK cells.

[c] No antiviral activity was observed up to a concentration of 1.0×10^{-3} mM."