Synthesis of Potent C_2-Symmetric, Diol-Based HIV-1 Protease Inhibitors. Investigation of Thioalkyl and Thioaryl P1/P1′ Substituents

Anna Mühlman,[†] Björn Classon,[†,#] Anders Hallberg,[‡] and Bertil Samuelsson*[,†,#]

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden, and Department of Organic Pharmaceutical Chemistry, BMC, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden

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The synthesis of novel, potent diol-based HIV-1 protease inhibitors, having either -SAr, -SCH_2-Ar, or -SCH_2R groups as P1/P1′ substituents is described. They can be prepared using a straightforward synthesis involving a thiol nucleophilic ring opening of a diepoxide. Inhibitor **13** was found to be a potent inhibitor of HIV-1 PR, showing good antiviral activity in a cell-based assay.

Introduction

The human immunodeficiency virus type 1 (HIV-1), the causative agent of acquired immunodeficiency syndrome (AIDS),[1−5] encodes for an aspartic protease shown to be essential for the formation of mature, infectious virus.[6−8] Intense efforts based on inhibiting this essential protease have been documented in numerous reports[9−15] and resulted in drugs on the market. At present, five protease inhibitors are approved by the U.S. Food and Drug Administration (FDA): saquinavir,[16] nelfinavir,[17] ritonavir,[18] indinavir,[19,20] and amprenavir.[21]

Despite efforts to develop C_2-symmetric inhibitors stimulated by the C_2-symmetric dimeric nature of the HIV-1 protease,[22] the marketed protease inhibitors are all nonsymmetric.

We have previously demonstrated that L-mannaric acid is a suitable scaffold for the design and synthesis of potent carbohydrate-based C_2-symmetric HIV-1 protease inhibitors.[23] Compounds **1** and **2** (Figure 1), in particular, have been shown to be potent inhibitors in vitro. This class of compounds comprises -OCH_2Ar groups as P1/P1′ substituents.

We have now extended the SAR studies of these promising lead inhibitors, and we herein describe a novel and straightforward synthesis of the thio analogues corresponding to inhibitors **1** and **2** containing either -SAr, -SCH_2Ar, or -SCH_2R groups as P1/P1′ substituents.

Results and Discussion

Chemistry. The starting material (2*S*,3*R*,2′*S*,3′*R*)-3′-hydroxymethyl-([2,2′]bioxiranyl-3-yl)-methanol **3** was synthesized in three steps, with an overall yield of 57% from commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol, according to the procedure described by Tipson and Cohen.[24]

Oxidation of diol **3** was first attempted with 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO)-NaOCl.[25,26] However, the diacid **4** proved difficult to extract from the aqueous layer, resulting in only a modest yield of **4** (45%). On the other hand, oxidation of diol **3** using $RuCl_3$ and H_5IO_6 in $CH_3CN-CH_2Cl_2-H_2O$ 2:2:3 proceeded smoothly, delivering pure diacid **4** in 86% yield (Scheme 1).[27] Subsequent couplings of diacid **4** with the selected amines (1*S*,2*R*)-1-amino-2-indanol and H-Val-NHMe were performed using benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) and *N*,*N*-ethyldiisopropylamine (DIEA) in CH_2Cl_2.[28,29] The diamides **5** and **6** were collected as white precipitates from the reaction mixture in 80% and 94% yield, respectively.

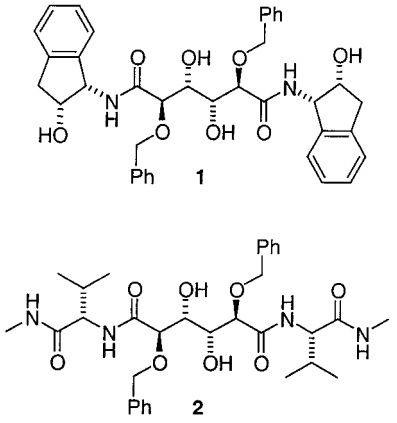

Figure 1.

Finally, the diepoxides **5** and **6** were reacted with selected thiols, in the presence of NaH in THF, to produce the target molecules **7**−**13** and **14**−**16** in excellent yields and regioselectivity (Table 1).[27,30,31] This reaction was conducted using two different methods (I and II). In method I, NaH (1.5 equiv) was added to the thiol (3 equiv) in DMF at −70 °C. Diamide **5** (1 equiv) was then added, and the temperature was allowed to rise slowly to −10 °C. The alternative method II was subsequently developed for thiols giving poor or no yield at all of products with method I. For method II, NaH (0.3 equiv) was added to a solution of thiol (3 equiv) and diamide **5** or **6** (1 equiv) in DMF at room temperature. Due to the propensity for racemization, the diamide **6** was only reacted with slightly acidic thiols ($pK_a < 7$).

Structure−Activity Relationship. The synthesized compounds can be viewed as falling into two categories, i.e., inhibitors **7**, **9**, **11**, **13**, and **14**−**16** falling into the

* To whom correspondence should be addressed. Phone: +46 8 6083100. Fax: +46 8 6083199. E-mail: bertil.samuelsson@medivir.se.
† Stockholm University.
# Additional address: Medivir AB, Lunastigen 7, SE-141 44 Huddinge, Sweden.
‡ Uppsala University.

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Scheme 1. Synthesis of HIV-1 Protease Inhibitors

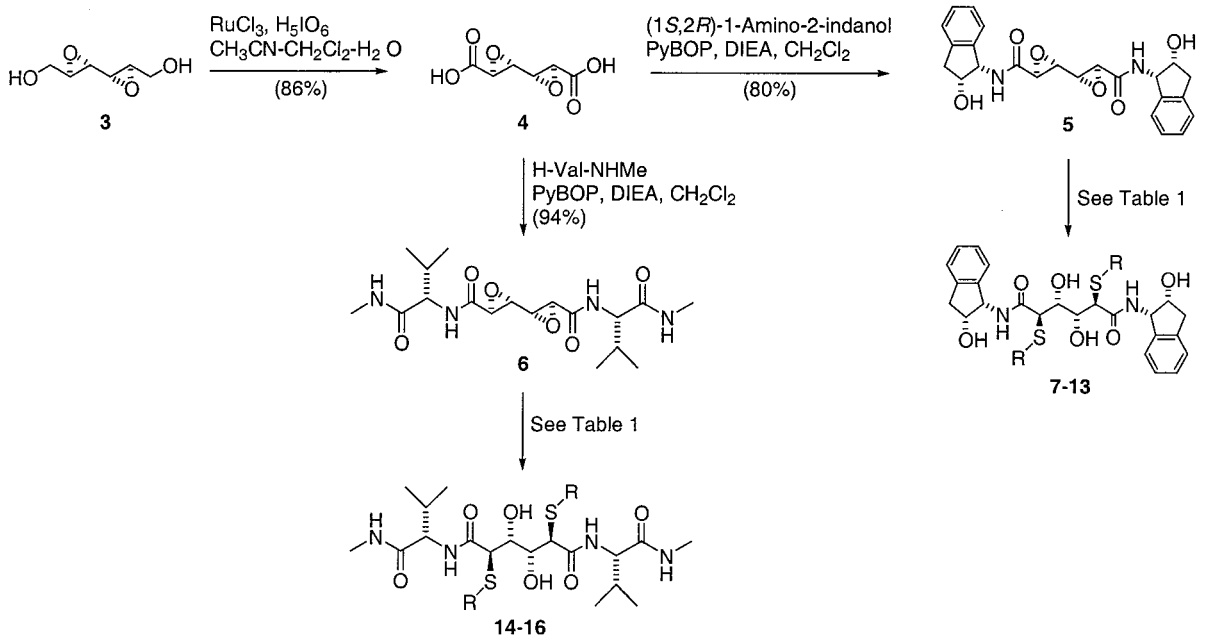
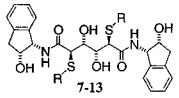


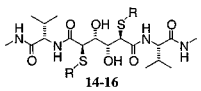
Table 1. Structures, Methods, Yields, and Inhibitory Activities

Compound number	K_i (nM)	ED_{50} (μM)
1[a]	0.60	0.096
2[a]	0.80	1.3



7-13

RSH	Compound number	pKa[b] RSH	Method/ Work-up	Yield (%)	K_i (nM)	ED_{50} (μM)
	7	6.6	II/A	74	1.8	0.26
	8	9.7	I/A	67	2.8	1.1
	9	6.0	II/A	60	2.3	0.11
	10	9.2	I/A	84	4.3	0.21
	11	9.6	II/B	74	285	>10
	12	9.8	I/A	54	16	>10
	13	6.4	II/B	70	0.5	0.027



14-16

	14	6.6	II/B	84	1.8	6.3
	15	6.0	II/B	76	0.57	3.6
	16	6.4	II/B	88	1.0	4.2

[a] See Figure 1. [b] pK_a values were calculated using "pK_a Calculator v.4.5" from Advanced Chemistry Development (ACD), www.acdlabs.com/products. For more details about the methods and workup procedures, see the Experimental Section.

first category having -SAr groups, and the second category consisting of inhibitors **8**, **10**, and **12** having $-SCH_2Ar$ groups (**8** and **10**) or $-SCH_2CHCH_2$ (**12**) in the P1/P1′ position. The thio group has often been considered as a bioisostere of the ethylene group. For the present series of inhibitors, the thio group also appears to be bioisosteric to the oxy-methyl group as this substitution produces very potent inhibitors. We have observed that for analogues of **1** and **2** the substitution in the ortho position of the P1/P1′ benzyl groups, in particular with a fluoro substituent, leads to enhancements in antiviral activity.[32] This substitution pattern was consequently also included in the current series. Thus from comparing compounds **7** with **9** (ED_{50} = 0.26 μM cf. 0.11 μM), **8** with **10** (ED_{50} = 1.1 μM cf. 0.21 μM), and **14** with **15** (ED_{50} = 6.3 μM cf. 3.6 μM) it is evident that this beneficial effect also translates into the sulfur containing inhibitors. Compound **11**, having basic ionizable P1/P1′ groups, show weak enzyme inhibition which is consistent with the lipophilic character of the S1/S1′ subsites. Another general feature of inhibitors related to **1** and **2**, is that potent enzyme inhibitors having the L-valine methyl amide in the S2/S2′ binding pockets predict low antiviral activity compared to the aminoindanol group.[23] This can be rationalized from the comparably lower cell permeability of compounds **2** and **14**−**16** attributed to the more peptidic character, i.e., four amide bonds rather than two.[33−35] The thienyl compound **13** represents a new lead inhibitor for this class of compounds, showing antiviral activity (ED_{50} = 0.027 μM) comparable to the activity of the HIV-1 PR inhibitors available on the market, e.g., ritonavir (ED_{50} = 0.055 μM), indinavir (ED_{50} = 0.073 μM), and nelfinavir (ED_{50} = 0.056 μM).[36]

Conclusion

A promising new series of very potent carbohydrate-based HIV-1 protease inhibitors have been discovered. Moreover, a new synthetic route has been developed, making these inhibitors readily available in high yields in just a few chemical steps from commercially available materials, which will greatly facilitate further lead optimization work.

Experimental Section

HIV-1 Protease Inhibition. HIV-1 protease was cloned and heterologously expressed in *Escherichia coli*,[37] and K_i values were determined using a fluorometric assay (Table 1).[38]

In Vitro Anti-HIV Activity. The anti-HIV activity was measured in a HIV cytopathic assay in MT-4 cells where the effect was quantified using vital dye XTT.[39] The 50% inhibitory concentrations (ED_{50}) were calculated from the percent cytoprotection for individual compounds (Table 1).

General. All glassware was dried over an open flame before use in connection with an inert atmosphere. Concentrations were performed under reduced pressure at <40 °C (bath temperature). Thin-layer chromatography was performed using silica gel 60 F-254 plates with detection by UV and charring with 8% sulfuric acid. Silica gel (0.040−0.063 mm) was used for column chromatography. Me_4Si (0.0 ppm) was used as an internal standard in ^1H NMR, and Me_4Si or $CDCl_3$ (77.0 ppm) was used in ^{13}C NMR. Melting points are uncorrected. Yields are not optimized. Unless stated otherwise, all materials were obtained from commercial suppliers and used without further purification.

(2*S*,3*R*,2′*S*,3′*R*)-[2,2]Bioxiranyl-3,3′-dicarboxylic Acid (4). (2*S*,3*R*,2′*S*,3′*R*)-3′-Hydroxymethyl-([2,2′]bioxiranyl-3-yl)-methanol **3** (2.0 g, 13.7 mmol) was dissolved in a stirred mixture of CH_3CN (55 mL), CH_2Cl_2 (55 mL), and H_2O (82 mL). $RuCl_3$ hydrate (114 mg, 0.55 mmol, 0.04 equiv) and H_5IO_6 (15.6 g, 68.4 mmol, 5.0 equiv) were added. After vigorous stirring for 1 h and 15 min, TLC showed completion of the reaction (R_f 0.25, $CHCl_3$−MeOH 6:1). The reaction mixture was transferred to a separatory funnel and diluted with CH_2Cl_2, and the aqueous layer was extracted with EtOAc (6×). The combined organic layers were dried ($MgSO_4$), filtered through a pad of Celite, and concentrated to give a dark solid material, which was suspended in Et_2O and a minor amount of EtOAc. Filtration through a pad of Celite and concentration gave pure diacid **4** (2.04 g, 11.7 mmol, 86%) as white crystals: $[\alpha]^{20}_D$ +120 (*c* 0.89, MeOH); mp 184−85 °C; ^1H NMR (300 MHz, $CDCl_3$ and CD_3OD) δ 3.28 (s, 2H), 3.48 (d, 2 H, J = 0.55 Hz), 4.90 (bs, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$ and CD_3OD) δ 50.2, 54.1, and 169.4. Anal. ($C_6H_6O_6$) C, H.

(2*S*,2′*S*,3*S*,3′*S*)-[2,2′]Bioxiranyl-3,3′-dicarboxylic Acid Bis-[(2*R*)-hydroxy-(1*S*)-indanylamide] (5). PyBOP (12.2 g, 23.4 mmol, 2.0 equiv) and DIEA (4.1 mL, 23.5 mmol, 2 equiv) were added to a stirred suspension of diacid **4** (2.04 g, 11.7 mmol) in CH_2Cl_2 (140 mL) under a nitrogen atmosphere. The reaction mixture became clear followed by the formation of a white precipitate within 10 min. Subsequent addition of (1*S*,2*R*)-1-amino-2-indanol (3.8 g, 25.8 mmol, 2.2 equiv) together with DIEA (4.1 mL, 23.5 mmol, 2 equiv) dissolved the precipitate. A new white precipitate was formed, which after 1 h was filtered off and rinsed with cold CH_2Cl_2 to give the diamide **5** (4.08 g, 9.35 mmol, 80%) as an amorphous, white solid: $[\alpha]^{20}_D$ +97 (*c* 0.36, DMSO); ^1H NMR (300 MHz, DMSO-d_6) δ 2.83 (d, 2 H, J = 15.9 Hz), 3.07 (dd, 2 H, J = 4.67 and 15.9 Hz), 3.32 (s, 2 H), 3.77 (s, 2 H), 4.44 (d, 2 H, J = 3.85 Hz), 5.22 (d, 2 H, J = 3.85 Hz), 7.18−7.23 (m, 8 H) and 8.21 (d, 2 H, J = 8.52 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 39.3, 51.9, 55.0, 56.7, 71.8, 123.9, 124.7, 126.2, 127.3, 140.6, 141.3 and 166.2. Anal. ($C_{24}H_{24}N_2O_6$) C, H, N.

(2*S*,2′*S*,3*S*,3′*S*)-[2,2′]Bioxiranyl-3,3′-dicarboxylic Acid Bis-[(1*S*)-2-methyl-1-(methylcarbamoyl)propylamide] (6). PyBOP (3.67 g, 7.05 mmol, 2.0 equiv) and DIEA (1.2 mL, 6.89 mmol, 2 equiv) were added to a stirred suspension of diacid **4** (615 mg, 3.53 mmol) in CH_2Cl_2 (53 mL) under a nitrogen atmosphere. The reaction mixture became clear followed by the formation of a white precipitate within 10 min. Subsequent addition of H-Val-NHMe (1.01 g, 7.76 mmol, 2.2 equiv), together with DIEA (1.2 mL, 6.89 mmol, 2 equiv), dissolved the precipitate. A new transparent precipitate was formed, which after 1 h and 15 min was filtered off and rinsed with cold CH_2Cl_2 (3×) to give the diamide **6** (1.32 g, 3.31 mmol, 94%) as an amorphous, white solid: $[\alpha]^{20}_D$ +55 (*c* 0.65, DMF); ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (d, 12 H, J = 6.32 Hz), 1.94−1.99 (m, 2 H), 2.58 (s, 3 H), 2.59 (s, 3 H), 3.20 (s, 2 H), 3.66 (s, 2 H), 4.11 (d, 2 H, J = 7.83 Hz), 7.95 (s, 2 H) and 8.19 (d, 2 H, J = 8.52 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.9, 18.9, 25.2, 30.3, 51.5, 54.5, 57.7, 165.8 and 170.6.

A small portion was recrystallized from DMF to give the diamide as a white solid, which was subjected to elementary analysis. Anal. ($C_{18}H_{30}N_4O_6 \cdot {}^1/_2$DMF) C, H, N.

General Method for the Preparation of Compounds 8, 10, and 12. Method I. NaH (1.5 equiv) was added to a stirred solution of a thiol (3.0 equiv) in DMF (8 mL) at −70 °C, under a nitrogen atmosphere. After 10 min, diamide **5** (200 mg, 0.458 mmol, 1.0 equiv) was added, and the temperature was allowed to rise slowly. TLC showed completion of the reaction after 1.5 h when the temperature was between −20 °C and −10 °C.

General Method for the Preparation of Compounds 7, 9, 11, 13, and 14−16. Method II. NaH (0.3 equiv) was added to a stirred solution of diamide **5** (200 mg, 0.458 mmol, 1.0 equiv) or **6** (200 mg, 0.502 mmol, 1.0 equiv), the reaction mixture was heated with a heating gun in order to dissolve diamide **6**, and a thiol (3.0 equiv) in DMF (8 mL) was added at room temperature, under a nitrogen atmosphere. TLC showed completion of the reaction ($CHCl_3$−MeOH 9:1) after 1−21 h.

Workup Procedure A. The reaction mixture was transferred to a separatory funnel, diluted with saturated NH_4Cl, and extracted with toluene (2×) and EtOAc (2×). Drying ($MgSO_4$) and concentration gave a syrup, which was dried under reduced pressure overnight. Trituration from $CHCl_3$−Et_2O gave the target compounds **7**−**10** and **12**.

Workup Procedure B. The reaction mixture was concentrated, and the resulting syrup was dried under reduced pressure overnight. Purification by column chromatography (packed with $CHCl_3$ and eluted with $CHCl_3$−MeOH 20:1) and trituration from $CHCl_3$−Et_2O gave the target compounds **11**, **13**, and **14**−**16**.

***N*1,*N*6-Di[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-di(phenylsulfanyl)hexanediamide (7).** The title compound was prepared according to method II and workup procedure A, using thiophenol (141 μL, 1.33 mmol) with stirring for 1 h, and was isolated as a white precipitate in 74% yield (224 mg, 0.341 mmol): R_f 0.65 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +69 (*c* 0.93, $CHCl_3$−MeOH 1:1); ^1H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 2.93 (d, 2 H, J = 16.5 Hz), 3.12 (dd, 2 H, J = 5.13 and 16.5 Hz), 3.82 (s, 6 H), 4.11 (d, 2 H, J = 5.49 Hz), 4.34 (d, 2 H, J = 5.49 Hz), 4.53−4.56 (m, 2 H), 5.31 (d, 2 H, J = 4.76 Hz), 6.99 (d, 2 H, J = 7.32 Hz), 7.12−7.37 (m, 12 H) and 7.49−7.51 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD) δ 39.2, 56.1, 57.8, 72.0, 72.4, 123.9, 124.8, 126.6, 127.5, 127.8, 129.0, 131.4, 133.0, 139.6, 140.0 and 171.1. Anal. ($C_{36}H_{36}N_2O_6S_2 \cdot 1H_2O$) C, H, N.

***N*1,*N*6-Di[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-di(benzylsulfanyl)-3,4-dihydroxyhexanediamide (8).** The title compound was prepared according to method I and workup procedure A, using benzyl mercaptane (161 μL, 1.37 mmol), and was isolated as a white precipitate in 67% yield (210 mg, 0.307 mmol): R_f 0.65 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +37 (*c* 0.92, $CHCl_3$−MeOH 1:1); ^1H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 2.95 (d, 2 H, J = 16.5 Hz), 3.15 (dd, 2 H, J = 5.12 and 16.5 Hz), 3.51 (d, 2 H, J = 6.59 Hz), 3.89 (s, 4 H), 4.08 (bs, 6 H), 4.23 (d, 2 H, J = 6.23 Hz), 4.58−4.60 (m, 2 H), 5.32 (d, 2 H, J = 4.76 Hz), 7.22−7.36 (m, 17 H) and 7.56 (d, 1H, J = 8.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD) δ 35.4, 38.9, 50.9, 57.2, 70.5, 72.1, 123.7, 124.5, 126.2, 126.6, 127.4, 127.9, 128.4, 136.9, 139.7, 140.0, and 172.1. Anal. ($C_{38}H_{40}N_2O_6S_2 \cdot {}^1/_2H_2O$) C, H, N.

***N*1,*N*6-Di[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-di(2-fluorophenylsulfanyl)-3,4-dihydroxyhexanediamide (9).** The title compound was prepared according to method II and workup procedure A, using 2-fluorothiophenol (148 μL, 1.38 mmol) with stirring for 2 h and 45 min, and was isolated as a white precipitate in 60% yield (190 mg, 0.274 mmol): R_f 0.5 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +90 (*c* 0.83, $CHCl_3$−MeOH 1:1); ^1H NMR (300 MHz, $CDCl_3$−CD_3OD) δ 2.93 (d, 2 H, J = 16.8 Hz), 3.13 (dd, 2 H, J = 4.94 and 16.8 Hz), 4.11 (d,

2 H, J = 5.49 Hz), 4.38 (s, 4 H), 4.39 (d, 2 H, J = 5.49 Hz), 4.52−4.54 (m, 2 H), 5.27−5.32 (m, 2 H), 7.08−7.24 (m, 10 H), 7.31−7.39 (m, 2 H), 7.56−7.61 (m, 2 H) and 7.77 (d, 2 H, J = 8.79 Hz); ^{13}C NMR (75 MHz, $CDCl_3$−CD_3OD) δ 39.1, 52.0, 54.8, 57.6, 57.7, 71.6, 72.3, 115.4, 115.7, 119.4, 119.6, 123.8, 124.4 (2 C), 124.6, 126.4, 127.6, 130.0, 130.1, 134.5, 139.7, 139.8, 160.1, 163.3, and 170.9. Anal. ($C_{36}H_{34}F_2N_2O_6S_2$) C, H, N.

***N*1,*N*6-Di[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-di(2-fluorobenzylsulfanyl)-3,4-dihydroxyhexanediamide (10).** The title compound was prepared according to method I and workup procedure A, using 2-fluorobenzyl mercaptane (163 μL, 1.48 mmol), and was isolated as a white precipitate in 84% yield (276 mg, 0.383 mmol): R_f 0.5 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +33 (*c* 0.87, $CHCl_3$−MeOH 1:1); ^{1}H NMR (300 MHz, $CDCl_3$−CD_3OD) δ 2.95 (d, 2 H, J = 16.5 Hz), 3.16 (dd, 2 H, J = 4.95 and 16.5 Hz), 3.65 (d, 2 H, J = 7.42 Hz), 3.98 (s, 4 H), 4.36 (d, 2 H, J = 7.42 Hz), 4.58−4.61 (m, 2 H), 4.71 (s, 6 H), 5.35 (d, 2 H, J = 4.94 Hz), 7.00−7.20 (m, 4 H), 7.21−7.29 (m, 10 H), and 7.40−7.45 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$−CD_3OD) δ 29.1, 39.1, 52.2, 57.7, 57.8, 71.4, 72.4, 115.0, 115.3, 123.9, 124.1, 124.3, 124.8, 126.6, 127.7, 128.9, 129.0, 130.8, 139.8, 140.0, 158.8, 162.1, and 171.8. Anal. ($C_{38}H_{38}F_2N_2O_6S_2 \cdot 1^1/_2H_2O$) C, H, N.

***N*1,*N*6-Di[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-di(2-pyridylsulfanyl)hexanediamide (11).** The title compound was prepared according to method II and workup procedure B, using 2-mercaptopyridine (153 mg, 1.38 mmol) with stirring for 4 h, and was isolated as a white precipitate in 74% yield (224 mg, 0.340 mmol): R_f 0.54 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +160 (*c* 1.06, $CHCl_3$-MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 2.92 (d, 2 H, J = 16.5 Hz), 3.12 (dd, 2 H, J = 5.13 and 16.5 Hz), 3.56 (s, 4 H), 4.56−4.64 (m, 6 H), 5.33−5.36 (m, 2 H), 7.07−7.35 (m, 12 H), 7.54−7.58 (m, 2 H), 8.04 (d, 2 H, J = 8.42 Hz), and 8.35 (d, 2 H, J = 4.39 Hz); ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD) δ 39.2, 50.5, 58.0, 58.1, 71.4, 72.7, 120.6, 123.4, 124.2, 124.9, 126.7, 127.8, 136.8, 140.1, 149.1, 156.9, and 172.0. Anal. ($C_{34}H_{34}N_2O_6S_2 \cdot {}^1/_2H_2O$) C, H, N.

***N*1,*N*6-Di[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-di(allylsulfanyl)-3,4-dihydroxyhexanediamide (12).** The title compound was prepared according to method I and workup procedure A, using allyl mercaptane (110 μL, 1.37 mmol), and was isolated as a white precipitate in 54% yield (145 mg, 0.248 mmol): R_f 0.46 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +59 (*c* 0.84, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 2.95 (d, 2 H, J = 16.5 Hz), 3.16 (dd, 2 H, J = 5.13 and 16.8 Hz), 3.32 (d, 4 H, J = 7.32 Hz), 3.57 (d, 2 H, J = 6.59 Hz), 4.09 (bs, 4 H), 4.14 (s, 2 H), 4.28 (d, 2 H, J = 6.22 Hz), 4.60−4.62 (m, 2 H), 5.16 (d, 2 H, J = 9.89 Hz), 5.24 (dd, 2 H, J = 1.37 and 17.0 Hz), 5.36 (d, 2 H, J = 4.76 Hz), 5.80−5.90 (m, 2 H), and 7.21−7.30 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD) δ 34.7, 39.2, 51.1, 57.6, 71.5, 72.4, 118.1, 123.9, 124.9, 126.7, 127.8, 133.1, 140.0, 140.1, and 172.2. Anal. ($C_{30}H_{36}N_2O_6S_2 \cdot {}^1/_2H_2O$) C, H, N.

***N*1,*N*6-Di[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-di(thiophen-3-ylsulfanyl)hexanediamide (13).** The title compound was prepared according to method II and workup procedure B, using thiophene-2-thiol (130 μL, 1.37 mmol) with stirring for 21 h, and was isolated as a white precipitate in 70% yield (215 mg, 0.322 mmol): R_f 0.39 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +47 (*c* 0.47, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 2.94 (d, 2 H, J = 16.8 Hz), 3.14 (dd, 2 H, J = 4.76 and 16.8 Hz), 3.84 (d, 2 H, J = 6.59 Hz), 4.26 (bs, 6 H), 4.40 (d, 2 H, J = 6.23 Hz), 4.55−4.57 (m, 2 H), 5.32 (d, 2 H, J = 2.56 Hz), 7.02−7.05 (m, 2H), 7.19−7.29 (m, 10 H), and 7.44−7.47 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD) δ 39.1, 57.6, 70.8, 72.4, 124.1, 124.8, 126.6, 127.5, 127.7, 129.9, 131.0, 135.9, 139.9, and 171.1. Anal. ($C_{32}H_{32}N_2O_6S_4 \cdot {}^1/_2H_2O$) C, H, N.

***N*1,*N*6-Di-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-di(phenylsulfanyl)hexanediamide (14).** The title compound was prepared according to method II and workup procedure B, using thiophenol (155 μL, 1.46 mmol) with stirring for 2.5 h, and was isolated as a white precipitate in 84% yield (260 mg, 0.420 mmol): R_f 0.41 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +11 (*c* 0.83, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 0.85 (s, 3 H), 0.86 (s, 3 H), 0.87 (s, 3 H), 0.88 (s, 3 H), 2.13−2.21 (m, 2 H), 2.73 (s, 3 H), 2.74 (s, 3 H), 4.01 (d, 2 H, J = 5.49 Hz), 4.13 (dd, 2 H, J = 5.86 and 8.79 Hz), 4.27 (d, 2 H, J = 5.49 Hz), 4.51 (s, 6 H), 7.27−7.33 (m, 5 H), and 7.43−7.48 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$−CD_3OD) δ 17.1, 18.9, 25.6, 30.0, 55.0, 58.5, 71.7, 127.5, 128.8, 131.4, 132.7, 170.9, and 171.8. Anal. ($C_{30}H_{42}N_4O_6S_2$) C, H, N.

***N*1,*N*6-Di-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-di(2-fluorophenylsulfanyl)-3,4-dihydroxyhexanediamide (15).** The title compound was prepared according to method II and workup procedure B, using 2-fluorothiophenol (157 μL, 1.46 mmol) with stirring for 3 h 15 min, and was isolated as a white precipitate in 76% yield (251 mg, 0.383 mmol): R_f 0.42 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ +22 (*c* 0.93, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 0.87 (s, 3 H), 0.89 (s, 6 H), 0.90 (s, 3 H), 2.15−2.21 (m, 2 H), 2.74 (s, 6 H), 3.99 (d, 2 H, J = 5.13 Hz), 4.11 (d, 2 H, J = 6.23 Hz), 4.33 (d, 2 H, J = 5.13 Hz), 4.42 (s, 6 H), 7.07−7.13 (m, 4 H), 7.29−7.35 (m, 2 H), and 7.48−7.52 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD) δ 17.0, 18.7, 25.4, 29.8, 54.1, 58.4, 58.5, 71.6, 115.5, 115.7, 119.4, 119.5, 124.4, 130.1, 130.2, 134.6, 160.6, 163.0, 170.7, and 172.0. Anal. ($C_{30}H_{40}F_2N_4O_6S_2$) C, H, N.

***N*1,*N*6-Di-[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-di(thiophen-3-ylsulfanyl)-hexanediamide (16).** The title compound was prepared according to method II and workup procedure B, using thiophene-2-thiol (138 μL, 1.46 mmol) with stirring for 1 h, and was isolated as a white precipitate in 88% yield (279 mg, 0.442 mmol): R_f 0.29 ($CHCl_3$−MeOH 9:1); $[\alpha]^{20}_D$ −7.5 (*c* 0.86, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 0.90 (d, 2 H, J = 6.96 Hz), 0.96 (d, 2 H, J = 6.96 Hz), 2.14−2.22 (m, 2 H), 2.75 (s, 6 H), 3.72 (d, 2 H, J = 6.23 Hz), 4.14 (d, 2 H, J = 6.59 Hz), 4.35 (d, 2 H, J = 6.23 Hz), 4.38 (s, 6 H), 6.99−7.00 (m, 2 H), 7.18−7.19 (m, 2 H), 7.43−7.48 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$−CD_3OD) δ 17.1, 18.8, 25.4, 30.0, 56.7, 58.5, 70.3, 127.2, 129.4, 130.8, 135.8, 170.5, and 171.8. Anal. ($C_{26}H_{38}N_4O_6S_4$) C, H, N.

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Supporting Information Available: Analytical data of the compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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