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Stereoselective Synthesis of 3-Aminoindan-1-ones and Subsequent Incorporation into HIV-1 Protease Inhibitors

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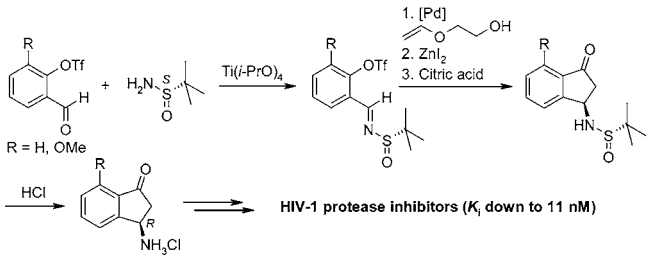
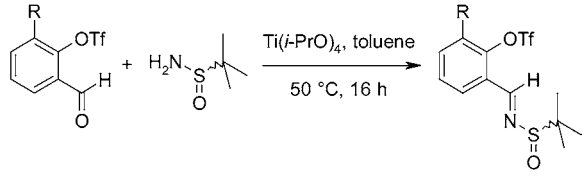


A new method for the stereoselective synthesis of 3-aminoindan-1-ones from triflates of salicylic sulfinyl imines and ethylene glycol vinyl ether has been developed. The reaction sequence starts with a regioselective Heck reaction followed by stereoselective Lewis acid mediated annulation. Acidic cleavage of the sulfinamides produced pure (*R*)- and (*S*)-3-aminoindan-1-ones, which were successfully isolated and incorporated into active HIV-1 protease inhibitors.

The indan skeleton is found in the P2 position in many potent aspartic protease inhibitors.[1] For example, the HIV-1 protease inhibitor indinavir incorporates a 1-amino-2-hydroxyindan fragment.[2] Importantly, Lyle et al. revealed early that additional substituents at the 3-position of the latter bicyclic ring system were well tolerated in HIV-1 protease inhibitors.[3] Thus, in our ongoing medicinal chemistry program aimed at developing improved HIV-1 protease inhibitors,[4] we sought a method that allowed stereoselective generation of 3-aminoindan-1-ones since modeling suggested that these groups might be well accommodated in the S2 site of the HIV-1 protease.

SCHEME 1. Synthesis of Sulfinyl Imines



1a R = H **(*R*)-2**
1b R = OMe **(*S*)-2**

(*R*)-3a: 96% R = H
(*S*)-3a: 89% R = H
(*R*)-3b: 93% R = OMe
(*S*)-3b: 94% R = OMe

We decided to further develop our previously reported multicomponent palladium-mediated method for the synthesis of racemic masked 3-aminoindan-1-ones from salicylic aldehyde triflates, ethylene glycol vinyl ether, and nucleophilic amines.[5] By replacing the formyl group by enantiopure *tert*-butyl sulfinyl imine, we hoped to achieve a diastereoselective reaction.

Enantiopure sulfinyl imines have been used in the stereoselective synthesis of a wide range of different amines.[6] We herein report on a novel synthetic route to chiral 3-aminoindan-1-ones, employing *tert*-butyl sulfinyl imine as the chiral handle, and their subsequent use as P2 substituents in HIV-1 protease inhibitors.

The enantiopure (*R*)- and (*S*)-sulfinyl imines (**3a**,**b**) were prepared in high yields by a Lewis acid mediated (Ti(*i*-PrO)$_4$) condensation reaction between salicylic aldehyde triflates (**1a**,**b**)[7] and *tert*-butyl sulfinamides, **(*R*)-2** and **(*S*)-2** (Scheme 1).[6i]

The subsequent annulation reaction was performed in a one-pot, two-step sequence (Scheme 2). First, ethylene glycol vinyl ether (**4**) was α-arylated via a ligand-controlled Heck reaction.[8] A mixture of the aromatic triflate (**3**) (1 equiv), ethylene glycol vinyl ether (3 equiv), Pd(OAc)$_2$/DPPP (0.05/0.1 equiv), and triethylamine (1.5 equiv) in acetonitrile was heated at 100 °C for 45 min, giving the intermediate annulation precursor (**5**). The product of the regioselective Heck arylation was not isolated but directly cyclized to the acetal-protected indan-1-one (**6**) in a Lewis acid mediated process. The double ring closure was believed to occur as previously reported for salicylic aldehydes (Scheme 2).[5,9]

To improve the process, different Lewis acids were investigated. After ring closure the crude reaction mixtures were

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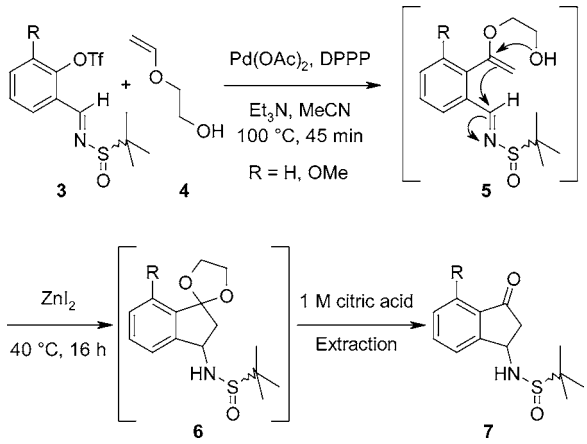
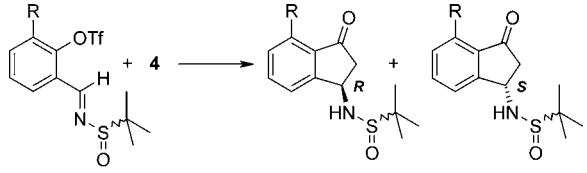
SCHEME 2. One-Pot Synthesis of 3-Sulfinamidoindan-1-ones



SCHEME 3



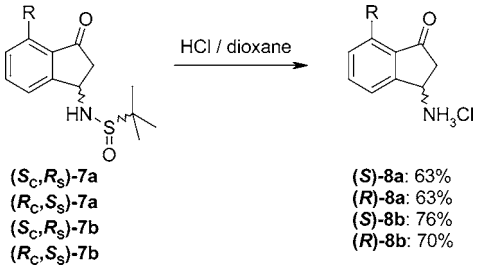
		R_C:S_C
(*R*)-**3a**	R = H	(*R*$_S$)-**7a**: 73%, 21:79
(*S*)-**3a**	R = H	(*S*$_S$)-**7a**: 70%, 74:26
(*R*)-**3b**	R = OMe	(*R*$_S$)-**7b**: 60%, 18:82
(*S*)-**3b**	R = OMe	(*S*$_S$)-**7b**: 60%, 83:17

analyzed with ^{1}H NMR, using 2,3-dimethylnaphthalene as internal standard, to determine the yield and the ratio of indanone diastereoisomers **7**. The choice of Lewis acid was found to affect both the yield and the stereoselectivity of the reaction. Strong Lewis acids, such as BCl_3SEt_2 and BBr_3SEt_2, decomposed the uncyclized vinyl ether (**5**), and no product was observed. BF_3-OEt_2 and TBDMSOTf produced a mixture of the acetal (**6**) and the deprotected indanone (**7**), with poor stereoselectivity. $ZnCl_2$, $ZnBr_2$, $ZnOTf_2$, several lanthanide triflates, and other Lewis acids were also tested, but no improvement in the diastereoselectivity was achieved. Finally, ZnI_2 was identified as the most selective catalyst. After further efforts, 1.5 equiv of ZnI_2, compared to the sulfinyl imine, and a temperature of 40 °C overnight were identified as suitable standard conditions for selective cyclization. To facilitate product separation, the acetal group was removed by extraction with 1 M citric acid before purification (Scheme 2).

The reactions were conducted with two different salicylic triflates, the unsubstituted (**1a**) and the 6-methoxy substituted (**1b**), using both the (*R*)- and the (*S*)-*t*-butylsulfinamide. In the related annulation of salicylic aldehydes,[9] the 6-methoxy-substituted salicylic substrate reacted faster in the ring closure due to electronic effects. We were therefore interested in investigating whether this activation might affect the stereoselectivity when using sulfinyl imines.

The preparative results are outlined in Scheme 3. All four reaction sequences gave **7** in combined R_C/S_S overall yields between 60 and 73%. Unfortunately, we were not able to achieve a maximum ratio of the diastereoisomers greater than 83:17. On the positive side, the two isomers were conveniently separated by standard silica flash chromatography. Thus, the isolated yields of the major isomers were between 49 and 58%.

SCHEME 4



(*S*$_C$,*R*$_S$)-**7a**
(*R*$_C$,*S*$_S$)-**7a**
(*S*$_C$,*R*$_S$)-**7b**
(*R*$_C$,*S*$_S$)-**7b**

(*S*)-**8a**: 63%
(*R*)-**8a**: 63%
(*S*)-**8b**: 76%
(*R*)-**8b**: 70%

The methoxy substituent had no major effect on the stereoselectivity or the yield of the reaction. The 3-aminoindane-1-ones were finally isolated as enantiopure hydrochloride salts (**8**) after acidic treatment of the sulfinamides (Scheme 4).

To determine the absolute configuration of the products, pure compounds **(*S*$_C$,*R*$_S$)-7a** and **(*R*$_C$,*S*$_S$)-7a** were studied using X-ray crystallography. The obtained structures revealed that when the *R*-isomer of the sulfinamide was used, *S*-aminoindane-1-one was formed as the major isomer.

Next, we focused on incorporating our tailor-made building blocks into linear HIV-1 protease inhibitors. The *C*2-symmetric inhibitor **14** was synthesized according to a previously reported method,[10] via ring opening of the key intermediate **9**, to serve as a reference inhibitor. The 3-aminoindan-1-ones **(*S*/*R*)-8a** were desalted and reacted with the bis-lactone **9** (Scheme 5). A mixture of the *C*2-symmetric compounds **(*S*/*R*)-11** and the mono-opened bis-lactone **10** was obtained. After crude purification, the mono-opened products were further reacted with indanolamine (**12**) to obtain the asymmetric compounds **(*S*/*R*)-13a**. Surprisingly, the methoxy-substituted indanones **(*S*/*R*)-8b** did not produce any di-opened products after reaction with the bis-lactone. As for the indanones **(*S*/*R*)-8a**, the mono-opened products were further reacted with indanolamine after crude purification to obtain the asymmetric compounds **(*S*/*R*)-13b**. The outcome of the reactions and the results of the biological tests are depicted in Scheme 5.

All compounds **11**, **13**, and **14** were tested in an HIV-1 protease assay.[11] The reference inhibitor (**14**) was found to have a K_i value of 1.6 nM. Replacing one of the indanolamines in the P2/P2′ positions by aminoindanone resulted in a 10-fold decrease in the activity of the *R*-isomer. The *S*-isomer was a further 10 times less active than the *R*-isomer. These results were consistent for both the unsubstituted and the methoxy-substituted aminoindanones. The *C*2-symmetric compounds **(*S*/*R*)-11**, where the P2/P2′ indanolamine had been replaced by aminoindanone on both sides of the inhibitor, were found to be inactive in the HIV-1 protease assay (Scheme 5).

The results from the biological testing are in accordance with what could be expected from the stereochemistry of the aminoindanones used. In the most active inhibitors, **(*R*)-13a** and **(*R*)-13b**, the configuration of the aminoindanones is the same as the configuration of the indanolamine P2/P2′ subunits of the highly active inhibitor **14**.

In conclusion, we have developed a new method for the stereoselective synthesis of 3-aminoindan-1-ones from salicylic

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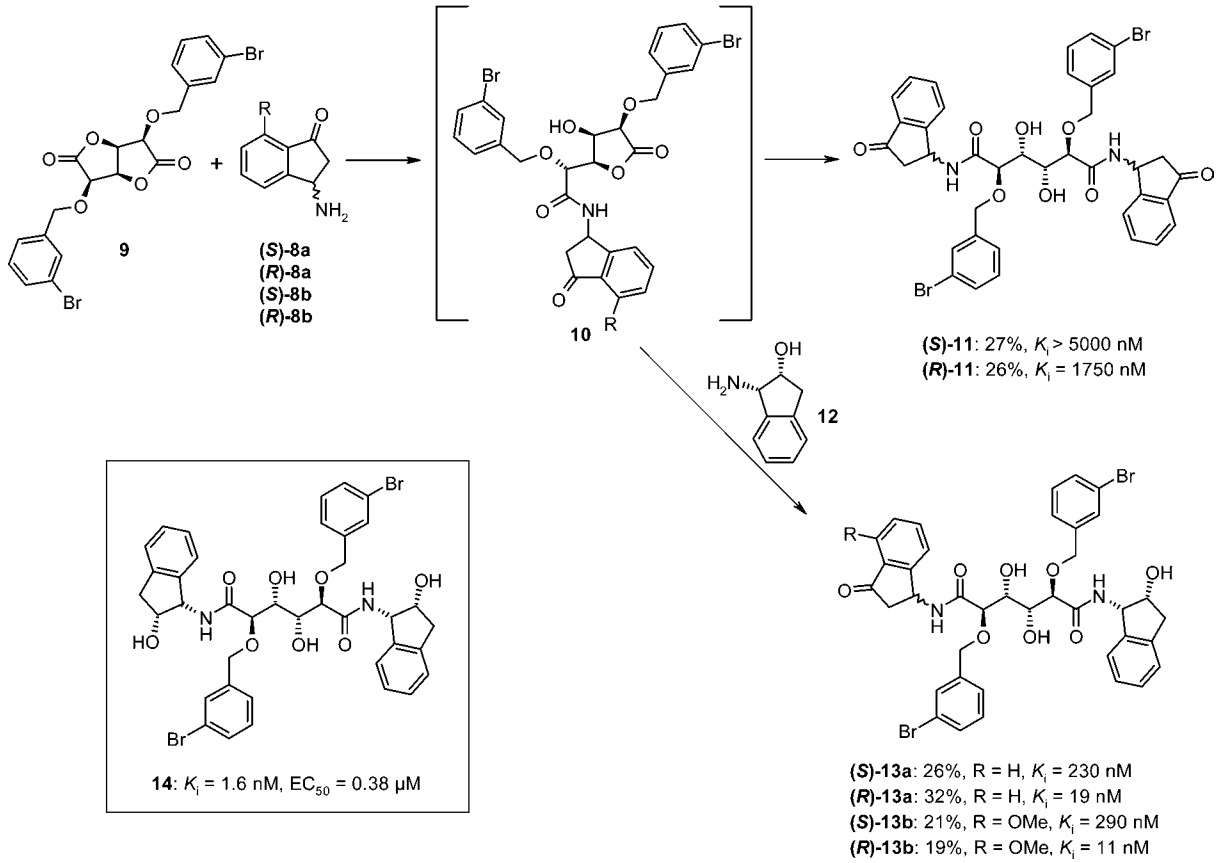
SCHEME 5. Synthesis of HIV-1 Protease Inhibitors



aldehydes using enantiopure *tert*-butyl sulfinamide as the chiral auxiliary. The reaction sequence involves regioselective Heck arylation of ethylene glycol vinyl ether with triflates of salicylic sulfinyl imines and subsequent in situ annulation. An application of this new chemistry was demonstrated by incorporating the pure (*R*)- and (*S*)-3-aminoindan-1-ones into HIV-1 protease inhibitors, giving K_i values down to 11 nM.

Experimental Section

General Experimental Procedure for the Synthesis of Sulfinyl Imines (3). The salicylic aldehyde triflate (**1**) (7.50 mmol), 2-methyl-2-propanesulfinamide (8.25 mmol, 1.00 g), and Ti(O-*i*-Pr)$_4$ (11.3 mmol, 3.36 mL) were dissolved in toluene (20 mL). The reaction mixture was stirred at 50 °C overnight and then quenched with $NaHCO_3$ (aq) (100 mL). The precipitation was removed by filtration and washed with toluene (40 mL). After dilution with toluene (40 mL), the phases were separated. The organic phase was washed with $NaHCO_3$ (aq) (2 × 50 mL), and the combined water phases were extracted with toluene (20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and evaporated. No further purification was needed.

Trifluoromethanesulfonic Acid 2-{[(*S*)-2-Methylpropane-2-sulfinylimino]-methyl}-phenyl Ester ((*S*)-3a). The title compound was afforded in 89% yield as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (s, 9H), 7.38 (dd, J = 1.2, 8.3 Hz, 1H), 7.47 (dddd, J = 0.6, 1.2, 7.4, 7.8 Hz, 1H), 7.58 (ddd, J = 1.8, 7.4, 8.3 Hz, 1H), 8.07 (dd, J = 1.8, 7.8 Hz, 1H), 8.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.8, 58.5, 118.8 (q, J = 320 Hz), 122.6, 127.1, 129.0, 130.7, 134.0, 148.8, 156.8. MS (ESI+): m/z 358 $(M + 1)^+$. Anal. Calcd for $C_{12}H_{14}F_3NO_4S_2$: C, 40.3; H, 4.0; N, 3.9. Found: C, 40.0; H, 3.8; N, 3.7. $[\alpha]^{20}_D$ +76.0 (*c* 1.07, MeOH).

Trifluoromethanesulfonic Acid 2-Methoxy-6-{[(*S*)-2-methylpropane-2-sulfinylimino]-methyl}-phenyl Ester ((*S*)-3b). The title compound was afforded in 94% yield as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (s, 9H), 3.95 (s, 3H), 7.19 (dd, J = 1.6, 8.3 Hz, 1H), 7.40 (ddd, J = 0.8, 8.0, 8.3 Hz, 1H), 7.63 (dd, J = 1.6, 8.0 Hz, 1H), 8.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.8, 56.7, 58.5, 116.6, 118.8 (q, J = 320 Hz), 121.0, 128.1, 129.1, 138.6, 152.1, 156.9. MS (ESI+): m/z 388 $(M + 1)^+$. Anal. Calcd for $C_{13}H_{16}F_3NO_5S_2 \cdot {}^1/_3H_2O$: C, 39.7; H, 4.3; N, 3.6. Found: C, 39.8; H, 3.9; N, 3.2. $[\alpha]^{20}_D$ +100.7 (*c* 1.05, MeOH).

General Experimental Procedure for the Synthesis of 2-Methylpropane-2-sulfinic Acid (3-Oxoindan-1-yl)-amides (7). Compound **3** (2.0 mmol) was dissolved in MeCN (15 mL) in a reaction tube. Ethylene glycol vinyl ether (6.0 mmol, 540 μL), Et_3N (3.0 mmol, 400 μL), $Pd(OAc)_2$ (100 μmol, 23 mg), and DPPP (200 μmol, 83 mg) were added. The reaction tube was sealed with a screw cap, and the reaction was heated at 100 °C. After 45 min, the reaction mixture was allowed to cool to room temperature. ZnI_2 (3.0 mmol, 960 mg) was added, and the reaction mixture was stirred at 40 °C overnight. The reaction was quenched with $NaHCO_3$ (aq) (15 mL). The precipitation was removed by filtration and washed with MeCN (5 mL) and EtOAc (20 mL). The aqueous phase was removed, and the organic phase was extracted with 1 M citric acid (40 mL) to remove the acetal. The acidic water phase was extracted with EtOAc (2 × 20 mL), and the combined organic phases were washed with brine (10 mL) and evaporated. The crude product was purified with flash chromatography (silica, 2−10% MeOH in EtOAc).

(*S*)-2-Methylpropane-2-sulfinic Acid ((*R*)-3-Oxoindan-1-yl)-amide ((R_C,S_S)-7a). The title compound was afforded in 52% yield as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (s, 9H), 2.75 (dd, J = 3.6, 19.3 Hz, 1H), 3.28 (dd, J = 7.3, 19.3 Hz, 1H), 3.50 (d, J = 10.0 Hz, 1H), 5.02 (ddd, J = 3.6, 7.3, 10.0 Hz,

1H), 7.49 (m, 1H), 7.65−7.70 (m, 2H), 7.77 (dm, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.9, 47.0, 54.9, 56.7, 123.6, 126.6, 129.7, 135.4, 136.9, 154.2, 203.0. Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.2; H, 6.9; N, 5.6. HRMS (M + 1): Calcd, 252.1058; Found, 252.1059. $[\alpha]^{20}_D$ −75.9 (*c* 1.04, MeOH).

(*S*)-2-Methylpropane-2-sulfinic Acid ((*R*)-4-Methoxy-3-oxoindan-1-yl)-amide ((*R*$_C$,*S*$_S$)-7b). The title compound was afforded in 50% yield as a pale yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ: 1.28 (s, 9H), 2.68 (dd, J = 3.7, 18.7 Hz, 2H), 3.09 (dd, J = 7.5, 18.7 Hz, 1H), 3.89 (s, 3H), 4.90 (dd, J = 3.7, 7.5 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.67 (dd, J = 7.6, 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.1, 46.6, 54.7, 55.0, 56.4, 110.6, 117.9, 124.3, 137.3, 157.75, 157.79, 202.5. Anal. Calcd for $C_{14}H_{19}NO_3S\cdot{}^1/_2H_2O$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.5; H, 6.9; N, 4.9. HRMS (M + 1): Calcd, 282.1164; Found, 282.1162. $[\alpha]^{20}_D$ −13.5 (*c* 1.04, MeOH).

General Experimental Procedure for the Cleavage of the 2-Methylpropane-2-sulfinic Acid Amides. Compound **7** (0.80 mmol) was dissolved in dioxane, and 4.0 M HCl in dioxane (1.6 mmol, 400 μL) was added. After 30 min, the mixture was filtered and the precipitated salt was washed thoroughly with dioxane.

(*R*)-3-Aminoindan-1-one Hydrochloride ((*R*)-8a). The title compound was afforded in 63% yield as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ: 2.69 (dd, J = 3.0, 19.0 Hz, 1H), 3.24 (dd, J = 7.8, 19.0 Hz, 1H), 5.08 (dd, J = 3.0, 7.8 Hz, 1H), 7.67 (m, 1H), 7.82−7.87 (m, 2H), 7.92 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ: 41.2, 67.0, 123.7, 126.3, 130.7, 135.8, 137.3, 149.2, 201.2. MS (ESI+): m/z 148 (M + 1)$^+$. Anal. Calcd for $C_9H_{10}NOCl\cdot{}^1/_4H_2O$: C, 57.46; H, 5.63; N, 7.44. Found: C, 57.6; H, 5.2; N, 7.2. $[\alpha]^{20}_D$ −42.5 (*c* 1.03, MeOH).

(*R*)-3-Amino-7-methoxyindan-1-one Hydrochloride ((*R*)-8b). The title compound was afforded in 70% yield as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.64 (dd, J = 3.0, 18.8 Hz, 1H), 3.18 (dd, J = 7.8, 18.8 Hz 1H), 3.95 (s, 1H), 4.99 (dd, J = 3.0, 7.8 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.80 (dd, J = 7.6, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.6, 47.7, 55.3, 112.6, 117.5, 124.6, 138.1, 151.5, 158.4. MS (ESI+): m/z 178 (M + 1)$^+$. $[\alpha]^{20}_D$ +1.44 (*c* 1.04, MeOH).

General Experimental Procedure for the Synthesis of HIV-1 Protease Inhibitors 11 and 13. The 3-amino-1-indanone **8** (400 μmol) was extracted between 5 mL of 1 M NaOH and 2 × 2.5 mL of DCE. The combined organic phases were dried with K_2CO_3, and bislactone **9** (100 μmol, 85 mg) was added. The mixture was stirred at 50 °C overnight. The solvent was evaporated, and the residue was purified by preparative reversed-phase LC/MS to afford pure inhibitor **11** and almost pure intermediate **10**.

The intermediate **10** was dissolved in 0.5 mL of DCE, and (1*S*,2*R*)-1-amino-2-indanol (4 equiv) was added. The mixture was stirred at 50 °C overnight. DCE (4 mL) and 1 M citric acid (3 mL) were added, and the mixture was stirred at 50 °C for 30 min. The phases were separated, and the organic phase was washed with brine. The solvent was evaporated to afford compound **13**.

(2*R*,3*R*,4*R*,5*R*)-2,5-Bis-(3-bromobenzyloxy)-3,4-dihydroxyhexanedioic Acid Bis-[((*R*)-3-oxoindan-1-yl)-amide] ((*R*)-11). The title compound was afforded in 26% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.54 (dd, J = 3.8, 18.7 Hz, 2H), 3.03 (dd, J = 7.8, 18.7 Hz, 2H), 3.89−3.95 (m, 4H), 4.46 (app s, 4H), 4.81−4.84 (m, 2H), 5.56 (ddd, J = 3.8, 7.8, 8.5 Hz, 2H), 7.25−7.35 (m, 4H), 7.44−7.52 (m, 6H), 7.59−7.70 (m, 6H), 8.68 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 44.3, 47.3, 70.1, 71.0, 80.7, 122.2, 123.0, 127.0, 127.2, 129.3, 130.9, 131.00, 131.01, 135.7, 137.1, 141.5, 155.9, 171.5, 204.1. Anal. Calcd for $C_{38}H_{34}Br_2N_2O_8\cdot H_2O$: C, 55.36; H, 4.40; N, 3.40. Found: C, 55.5; H, 4.2; N, 2.9. HRMS (M + 1): Calcd, 805.0760; Found, 805.0764. $[\alpha]^{20}_D$ +21.7 (*c* 0.97, DMSO-d_6).

(2*R*,3*R*,4*R*,5*R*)-2,5-Bis-(3-bromobenzyloxy)-3,4-dihydroxyhexanedioic Acid ((1*S*,2*R*)-2-Hydroxyindan-1-yl))-amide ((*S*)-3-Oxoindan-1-yl)-amide ((*R*)-13a). The title compound was afforded in 32% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.54 (dd, J = 3.9, 18.7 Hz, 1H), 2.80 (dd, J = 1.5, 16.5 Hz, 1H), 3.02 (dd, J = 7.8, 18.7 Hz, 1H), 3.05 (dd, J = 4.7, 16.5 Hz, 1H), 3.90−3.98 (m, 3H), 4.09 (d, J = 8.3 Hz, 1H), 4.43 (app dq, J = 1.5, 4.9 Hz, 1H), 4.47 (app s, 2H), 4.50 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.85−4.88 (m, 2H), 5.05 (d, J = 4.3 Hz, 1H), 5.25 (dd, J = 5.0, 8.8 Hz, 1H), 5.58 (ddd, J = 3.9, 7.8, 8.5 Hz, 1H), 7.11−7.36 (m, 8H), 7.44−7.55 (m, 5H), 7.61−7.70 (m, 3H), 7.84 (d, J = 8.8 Hz, 1H) 8.67 (d, J = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 44.3, 47.3, 57.4, 70.2, 70.3, 70.9, 71.0, 72.8, 80.2, 80.7, 122.20, 122.24, 123.0, 125.1, 125.5, 126.9, 127.0, 127.1, 127.2, 128.0, 129.3, 130.85, 130.90, 130.99, 131.00, 131.01, 131.05, 135.7, 137.0, 141.4, 141.5, 141.7, 142.7, 155.9, 171.47, 171.51, 204.1. HRMS (M + 1): Calcd, 807.0917; Found, 807.0934. $[\alpha]^{20}_D$ +17.6 (*c* 0.55, DMSO-d_6).

(2*R*,3*R*,4*R*,5*R*)-2,5-Bis-(3-bromobenzyloxy)-3,4-dihydroxyhexanedioic Acid ((1*S*,2*R*)-2-Hydroxyindan-1-yl))-amide ((*R*)-4-Methoxy-3-oxoindan-1-yl)-amide ((*R*)-13b). After further purification by preparative reversed-phase LC/MS, the title compound was afforded in 19% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.50 (dd, J = 4.2, 18.2 Hz, 1H), 2.82 (dm, J = 16.3 Hz, 1H), 2.91 (dd, J = 7.9, 18.2 Hz, 1H), 3.07 (dd, J = 5.0, 16.3 Hz, 1H), 3.84 (s, 3H), 3.92−3.98 (m, 3H), 4.10 (d, J = 8.0 Hz, 1H), 4.45 (m, 1H), 4.47 (app s, 2H), 4.51 (d, J = 11.8 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.82−4.92 (m, 2H), 5.06 (d, J = 4.3 Hz, 1H), 5.27 (dd, J = 5.0, 8.7 Hz, 1H), 5.48 (ddd, J = 4.2, 7.9, 8.5 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 7.12−7.36 (m, 9H), 7.45−7.49 (m, 2H), 7.52 (m, 1H), 7.56 (m, 1H), 7.60 (m, 1H), 7.85 (d, J = 8.8 Hz, 1H) 8.62 (d, J = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 44.7, 46.7, 49.3, 56.3, 57.5, 70.26, 70.28, 70.9, 71.0, 72.8, 80.3, 80.7, 111.4, 118.3, 122.21, 122.25, 124.9, 125.1, 125.5, 126.9, 127.17, 127.23, 128.0, 130.87, 130.92, 131.00, 131.01, 131.02, 131.07, 137.4, 141.4, 141.5, 141.7, 142.7, 157.5, 158.2, 171.4, 171.5, 200.9. HRMS (M + 1): Calcd, 837.1022; Found, 837.1017. $[\alpha]^{20}_D$ +24.2 (*c* 0.36, DMSO-d_6).

***N*1,*N*6-Bis[(1*S*,2*R*)-2-hydroxy-1-indanyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis(3-bromobenzyloxy)-3,4-dihydroxyhexane-1,6-diamide (14).** To a solution of bislactone **9** (1.80 g, 3.52 mmol) in 200 mL of 1,2-dichloroethane was added (1*S*,2*R*)-1-amino-2-indanol (2.10 g, 14.1 mmol). The mixture was stirred at 50 °C, and the reaction was monitored by TLC and analytical reversed-phase LC/MS. After 5 h, the solvent was removed under reduced pressure, and the residue was purified by silica flash column chromatography (5% MeOH in $CHCl_3$) to give **14** (1.30 g, 45%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.76 (dd, J = 16.6, 2.4 Hz, 2H), 3.02 (dd, J = 16.6, 5.5 Hz, 2H), 4.03 (d, J = 5.0 Hz, 2H), 4.27−4.20 (m, 4H), 4.56 (app dq, J = 5.2, 2.4 Hz, 2H), 4.62 (d, J = 11.9 Hz, 2H), 4.66 (d, J = 11.9 Hz, 2H), 4.78 (d, J = 3.8 Hz, 2H), 5.26 (dd, J = 8.7, 5.1 Hz, 2H), 7.28−7.15 (m, 12H), 7.42 (dt, J = 7.8, 1.8 Hz, 2H), 7.52 (t, J = 1.8 Hz, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 39.3, 58.0, 71.7, 72.5, 72.7, 122.9, 124.2, 125.5, 126.6, 127.3, 128.5, 130.5, 131.0, 131.5, 139.3, 139.8, 140.9, 171.3. MS (ESI+): m/z 809, 811, 813 (M + H)$^+$. Anal. Calcd for $C_{38}H_{38}Br_2N_2O_8\cdot{}^1/_2H_2O$: C, 55.69; H, 4.80; N, 3.42. Found C, 55.6; H, 5.1; N, 3.3.

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Supporting Information Available: Complete experimental details with full analytical characterization of all new compounds. CIF files and ORTEP plots for compounds **(*S*$_C$,*R*$_S$)-7a** and **(*R*$_C$,*S*$_S$)-7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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