Synthesis of Novel, Potent, Diol-Based HIV-1 Protease Inhibitors via Intermolecular Pinacol Homocoupling of (2*S*)-2-Benzyloxymethyl-4-phenylbutanal

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The synthesis of novel, potent, diol-based HIV-1 protease inhibitors, having phenethyl groups ($-CH_2CH_2Ph$) in P1/P1′ position is described. An intermolecular pinacol homocoupling of (2*S*)-2-benzyloxymethyl-4-phenylbutanal **16** was the key step in the synthesis. From this reaction sequence four carba analogues, compounds **8a**, **8b**, **9a**, and **9b**, were prepared**,** having the inverted configuration of one or both of the stereogenic centers carrying the diol hydroxyls as compared to the parent series represented by inhibitors **6** and **7**. Inhibitor **8b** was found to be a potent inhibitor of HIV-1 protease (PR), showing excellent antiviral activity in the cell-based assay and in the presence of 40% human serum. The absolute stereochemistry of the central diol of the potent inhibitor (**8b**) was determined from the X-ray crystallographic structure of its complex with HIV-1 PR.

Introduction

The human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS).[1−5] The human immunodeficiency virus type 1 (HIV-1) encodes for an aspartic protease, which is essential for the formation of mature, infectious virus.[6−8] The intense efforts to discover inhibitors of this protease have resulted in numerous reports,[9−15] and efficacious drugs are on the market.[16] At present, five protease inhibitors are approved by the US Food and Drug Administration (FDA): saquinavir (**1**),[17] nelfinavir (**2**),[18] ritonavir (**3**),[19] indinavir (**4**),[20,21] and amprenavir (**5**)[22] (Figure 1). These inhibitors are all nonsymmetric, although early elegant efforts were made to take advantage of the C_2-symmetry of the HIV-1 protease.[23]

We have more recently discovered that L-mannaric acid is a promising scaffold for the design and synthesis of potent C_2-symmetric HIV-1 protease inhibitors.[24] Among these, compounds **6** and **7** in particular (Figure 2) have been shown to be potent HIV-1 protease inhibitors in vitro. The impact of the stereochemistry of the stereogenic centers carrying the central diol on the activity of inhibitor **7** has also been thoroughly investigated.[25] An unusual feature of these inhibitors is that they are readily available in just three chemical steps starting from commercially available materials.

Four of the HIV-1 PR inhibitors in clinic comprise a P1/P1′ benzyl substituent, while a benzyloxy group is present in the carbohydrate-based inhibitors. This difference raises the question as to the influence of the P1/P1′ oxygen atom on the anti-HIV activity for the latter class of inhibitors.

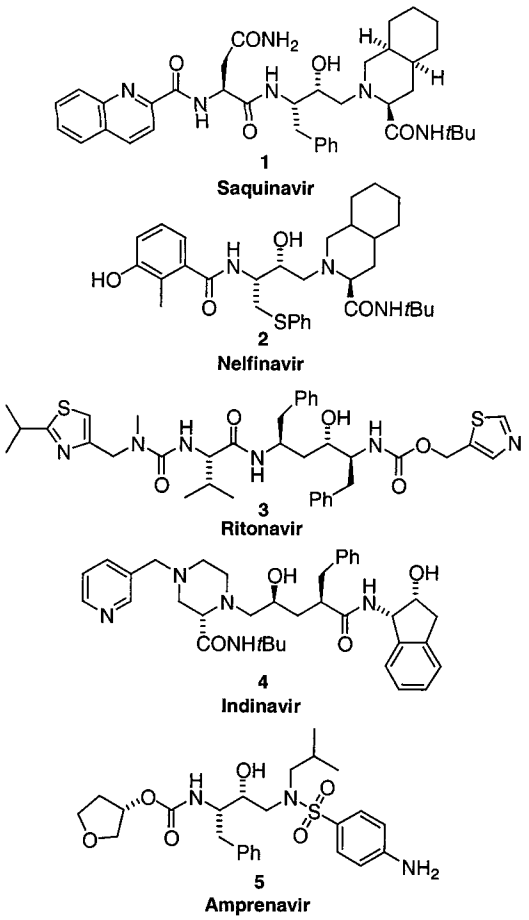

Figure 1. FDA-approved HIV-1 protease inhibitors.

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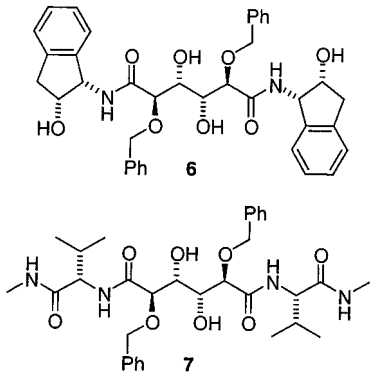


Figure 2.

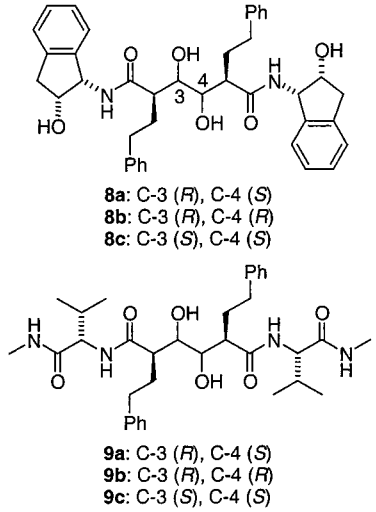


Figure 3.

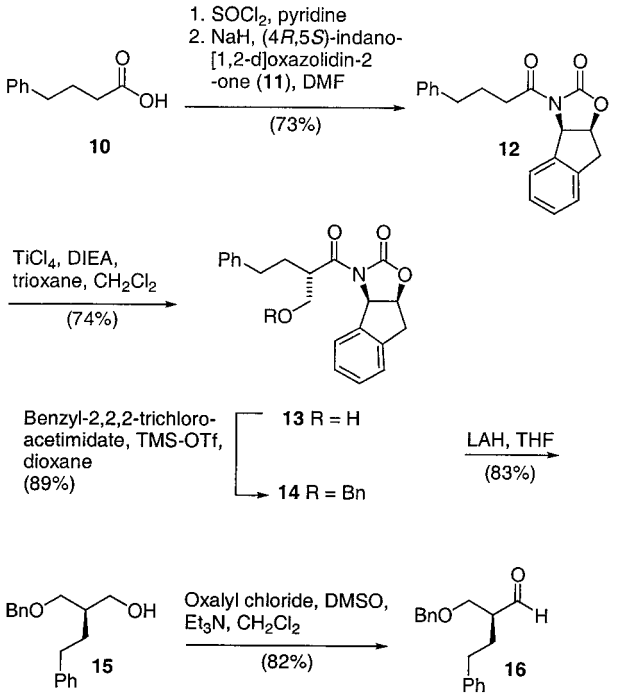
From examination of the X-ray crystallographic structure of the HIV-1 protease complex of **6** and the isoleucine analogue of **7**, it is evident that the hydroxyl groups of the central diol do not bind symmetrically to the active site Asp 25/125 residues. One of the hydroxyl groups forms hydrogen bonds with both carboxyl groups, while the other hydroxyl group points away from the active site but still maintains one hydrogen bond to one of the Asp residues. It could thus be anticipated that the structural modification of atoms engaged in the anchoring of the P1/P1′ substituents to the backbone would have effects on the preferred chirality of the stereogenic centers carrying the central diol in this series. Thus, it seemed important to prepare the carba analogues to elucidate the SAR of the promising C_2-symmetric HIV-1 PR inhibitors.

We herein describe the synthesis of two out of three possible stereoisomers of the diol for the carba analogues of **6** and **7**. The pinacol homocoupling synthetic strategy provided an entry into the carba analogues **8a**, **8b** and **9a**, **9b** (Figure 3) that were synthesized and evaluated for anti-HIV activity. Compound **8b** was unexpectedly revealed to be a very potent inhibitor, even better than the parent inhibitor **6**.

Results and Discussion

Chemistry. 4-Phenylbutyric acid **10** was converted to the corresponding acid chloride in 98% yield using $SOCl_2$−pyridine (Scheme 1).[26] The chiral auxiliary, (4*R*,5*S*)-indano[1,2-*d*]oxazolidin-2-one (**11**), which was

Scheme 1

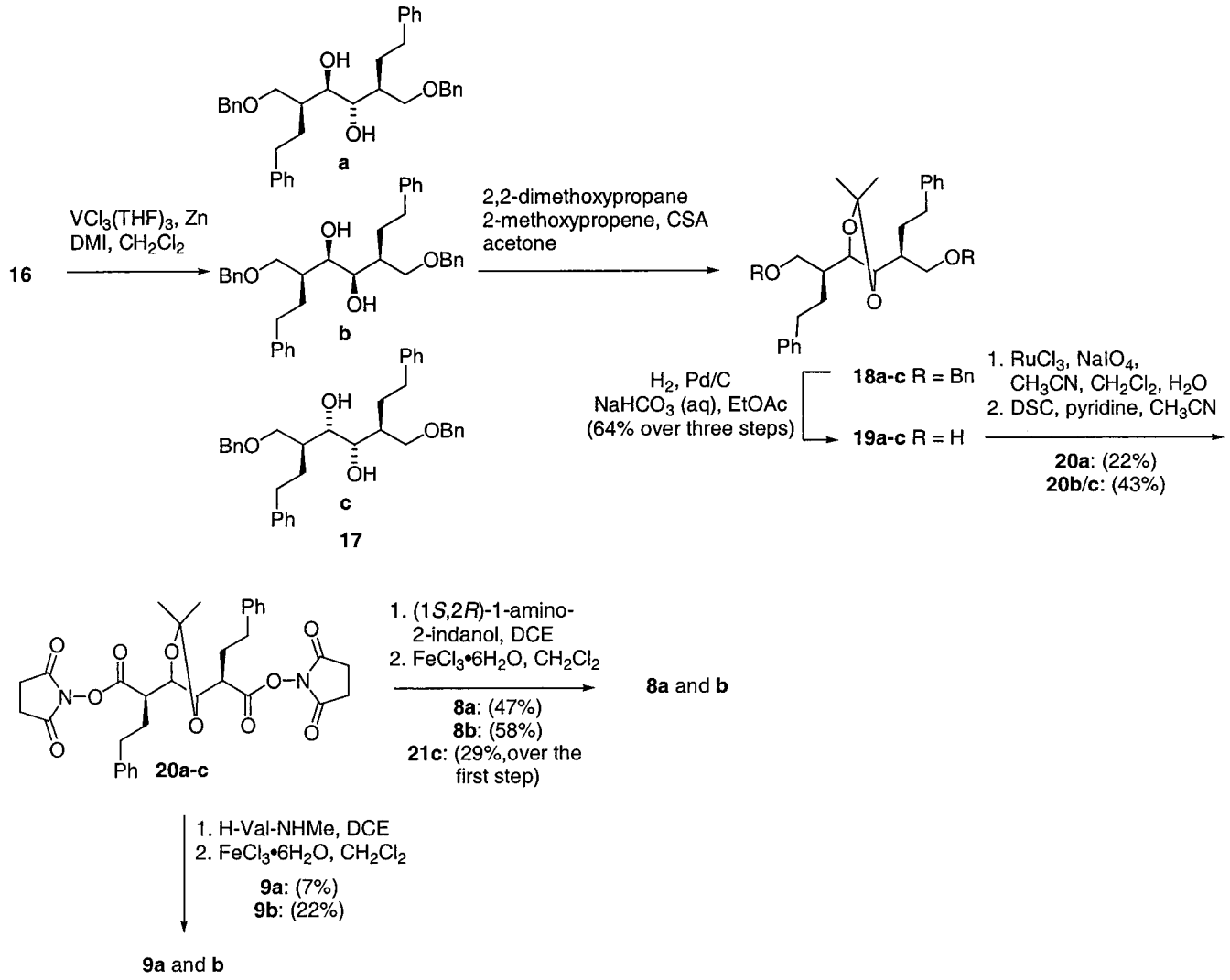


synthesized in 95% yield from (1*R*,2*S*)-1-amino-2-indanol by treatment with triphosgene and NEt_3 in CH_2Cl_2,[27,28] was coupled with the acid chloride in the presence of NaH in DMF to give **12** in 74% yield.[29,30] Hydroxymethylation of **12**, utilizing 1,3,5-trioxane in the presence of $TiCl_4$ and *N*-ethyldiisopropylamine (DIEA) in CH_2Cl_2 afforded 74% yield of diastereomerically pure (as determined by NMR) **13**.[31] It was observed that during acidic workup conditions, dimerization of **13**, via acetal formation, occurred to some extent. However, neutralization and immediate purification by silica gel column chromatography eliminated this side reaction. Benzylation of **13** with benzyl-2,2,2-trichloroacetimidate in dioxane with a catalytic amount of TMS−OTf produced **14** in 89% yield.[32,33] The subsequent reduction of **14** with LAH in THF gave 83% yield of enantiomerically pure (Mosher's ester methodology[34]) alcohol **15**, which was oxidized to (2*S*)-2-benzyloxymethyl-4-phenylbutanal **16** (82% yield) by a Swern oxidation.[35]

The diols **17a**−**c** were synthesized via a vanadium(II)-promoted pinacol homocoupling of aldehyde **16** (Scheme 2), using the vanadium(III) chloride−tetrahydrofuran complex ($VCl_3(THF)_3$), which was reduced by zinc dust in CH_2Cl_2, to form a dimeric vanadium(II) structure.[36] According to the literature, to achieve a high yield and stereoselectivity in cross-coupling reactions of this type, it is required of at least one of the aldehyde reactants to be activated, i.e., contain a carbonyl group, preferentially an amide or ester carbonyl, in the γ-position to allow for a vanadium chelation-accelerated process or, alternatively, that one of the aldehydes is present in excess.[37−39] The carbonyl group is proposed to form a seven-membered chelate ring with the vanadium(II) complex, thereby enhancing the rate of the reaction and improve stereoselectivity.

The aldehyde **16** lacks a carbonyl group in γ-position, and there is no preference for formation of this type of related complex in the present case. On the other hand, the ether oxygen oxygen atom in aldehyde **16** might

Scheme 2



provide a substitute for the carbonyl group and a chelation, depicted in Figure 4, can be anticipated.[36] However, the pinacol homocoupling of aldehyde **16** provides equal amounts of **17a** and an inseparable mixture of compounds **17b**/**c**, suggesting that no chelation contributing to stereochemical induction is operating.

Several different experimental procedures for achieving this coupling have been described involving variations in (a) the relative amounts of reagents employed, (b) the temperature, (c) the procedure for workup, and (d) the presence or absence of external complexing agents.[40−42]

At first, we attempted 1.2 equiv of $VCl_3(THF)_3$ and 1.4 equiv of zinc dust in CH_2Cl_2 in the presence of excess of the complexing agent 1,3-dimethyl-2-imidazolidinone (DMI) and 1 equiv of aldehyde **16**, at room temperature for 4 h followed by workup under acidic conditions. Under these conditions, all possible isomers were formed, albeit in a low crude yield (38%). No improvement was encountered after a longer reaction time. The carboxylic acid derived from oxidation of aldehyde **16** constituted the main byproduct.

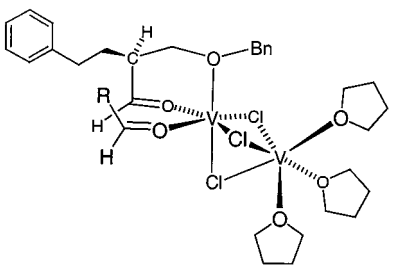


Figure 4.

Reaction with an excess amount of zinc dust present (2 equiv instead of 1.4 equiv) and reaction in a larger scale (2−4 g instead of 50−100 mg of **16**) resulted in significant improvements. Thus, this alteration changed the total crude yield to 81% and the carboxylic acid was not formed. Instead, a minor amount of alcohol **15** could be isolated (5%). The presence of excess zinc has previously been reported to enhance the rate and yield of sluggish reactions between nonchelating aldehydes and paraformaldehyde.[43] Regeneration of vanadium(II) ions from vanadium(III) products accounts for this observation. Our results indicate that employment of excess amounts of zinc is advantageous also for homocoupling of nonchelating aldehydes.

Diols **17a** were easily separated by silica gel column chromatography from the mixture of the two C_2-symmetric diastereomers **17b** and **17c**, which were used as such in the subsequent steps. The diols **17a** and the

mixture of **17b/c** were protected as isopropylidene ketals by treatment with 2,2-dimethoxypropane and 2-methoxypropene in acetone containing (±)-camphor-10-sulfonic acid (CSA). Subsequent, debenzylation of **18a**−**c** using H_2, Pd/C in EtOAc in the presence of $NaHCO_3$ and a small quantity of water gave compounds **19a**−**c** in an overall yield of 64% for the three steps. Oxidation of compounds **19a**−**c** was accomplished with $RuCl_3$ and $NaIO_4$ in $CH_3CN-CH_2Cl_2-H_2O$ 2:2:3.[44] The corresponding dicarboxylic acids were immediately converted to the active esters by treatment with *N*,*N*-disuccinimidyl carbonate (DSC) and pyridine in CH_3CN.[45] Diester **20a** was isolated in 22% overall yield for the two steps and **20b/c** in 43% yield. Compounds **20b** and **20c** were now easily separated by silica gel column chromatography, to give a 1:4 ratio of **20b** to **20c**. The absolute stereochemistry of compound **20b** was deducted from the X-ray crystallographic structure of the complex between compound **8b** and HIV-1 protease (see below).

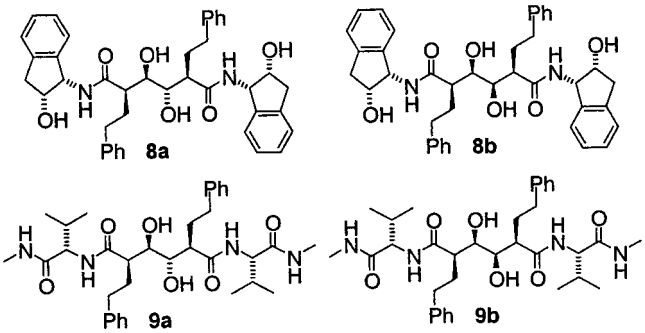
The preferred amines used in the subsequent couplings, (1*S*,2*R*)-1-amino-2-indanol and H-Val-NHMe, were selected on the basis of our previous work.[24] Each of compounds **20a**−**c** were thus coupled with (1*S*,2*R*)-1-amino-2-indanol in 1,2-dichloroethane (DCE) at 60 °C to give compounds **21a-c**.

The final deprotection of the isopropylidene groups proved to be a challenge. Hydrolysis using $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2[46] was initially attempted, for which good results have been obtained previously. Compound **21a** was successfully deprotected using this reagent to give 47% overall yield for the two steps of the unsymmetric target molecule **8a**. Deprotection of compound **21b**, using the same procedure with the modification that the solvent was coevaporated several times in order to remove the acetone formed in the reaction, yielded the C_2-symmetric target molecule **8b** in 58% overall yield for the two steps.

However, in the case of compound **21c**, which was isolated in 29% yield after the coupling reaction, the isopropylidene group could not be removed despite examining a wide series of deprotection procedures. $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2 failed to react, whereas *N*-bromosuccinimide in $CH_2Cl_2-H_2O$ 9:1 or 50% TFA in CH_2Cl_2 resulted in the formation of several unidentified byproducts with complete disapperance of **21c**. The acidic procedure used previously, i.e., 4% HCl/MeOH in CH_2Cl_2, initially appeared promising, but the only product that was isolated was the dilactone, formed by hydrolysis of both the isopropylidene group and the amide linkages followed by intramolecular lactonization. Coupling of **20a** and **20b** with H-Val-NHMe in DCE at 60 °C gave **23a** and **23b**, whereas the coupling of **20c** could not be achieved in this manner. Several side products were formed instead. Deprotection of compound **23a** and **23b** was accomplished employing the same procedure as for **8b**, which gave the unsymmetric compound **9a** in 7% overall yield for the two steps and the C_2-symmetric compound **9b** in 22% yield.

Anti-HIV-1 Activity and 3-D Structure. The target molecules **8a**, **8b** and **9a**, **9b** were tested for anti-HIV activity (Table 1). Surprisingly, compounds **8b** and **9b** were found to be very potent inhibitors (K_i = 1.1 and 0.40 nM, respectively) considering that they have the opposite configurations of the stereogenic centers carrying the central diols compared to inhibitor **6** and **7** (K_i = 0.60 and 0.80 nM, respectively).

Table 1. HIV-1 Protease Inhibitory Activities



compd	K_i (nM)	ED_{50} (μM)	ED_{50}+hs[b](μM)
6[a]	0.60	0.096	1.5
7[a]	0.80	1.3	34
8a	28	>10	15
8b	1.1	0.093	0.39
9a	112	>10	>10
9b	0.40	1.9	1.4

[a] See Figure 2. [b] hs = 50% human serum for **6** and **7** and 40% human serum for **8a**, **8b** and **9a**, **9b**.

These results can be compared to earlier findings,[25] where the diol epimer of inhibitor **7** was shown to be 100 times less active than inhibitor **7** itself. Kempf et al. have, on the other hand, reported that small differences in potencies can be observed between various diastereomeric diols, within certain series of inhibitors.[47,48]

Compound **8b** showed good antiviral activity (ED_{50} = 0.093 μM) in the cell-based assay and even more promising was the relatively small drop (3 times) in antiviral activity in the presence of 40% human serum (ED_{50}+40% hs = 0. 39 μM), whereas compound **9b** was found to be less active (ED_{50} = 1.9 μM) when tested in cell culture and also in the presence of 40% human serum (ED_{50}+40% hs = 1.4 μM).

To analyze the mode of binding to the HIV-1 protease (PR) for the most potent inhibitor **8b** and to confirm the absolute stereochemistry, **8b** was cocrystallized with HIV-1 PR and the structure solved by X-ray crystallography (Figure 5).

An overall similarity in binding conformation was observed with the recently published structure of the parent inhibitor **6**.[24] The inversion of configuration of the stereogenic centers carrying the central diol of inhibitor **8b** in comparison to inhibitor **6** was confirmed in the electron density map. Superimposition of the structures of **8b** and **6** clearly show this difference in configuration (Figure 6). The hydrogen-bond pattern of the central diol to the catalytic aspartate residues described previously was not affected with the change of configuration in **8b**.[24] As a consequence of the change in configuration, the P2′ substituent of **8b** does not reach as deep into the S2′/S3′ subsites as inhibitor **6** (Figure 7). The difference in positioning of the P2′ substituent (0.8 Å) influences the interactions to the S2′/S3′ subsites. The distances between the P2′ indanol hydroxyl group of inhibitor **8b** and the hydrogen-bond-accepting/-donating groups of Asp 129 (backbone nitrogen and Oδ2) increased by 0.4 Å, thereby exceeding optimal hydrogen-bond distances (3.14 and 3.24 Å, respectively). In

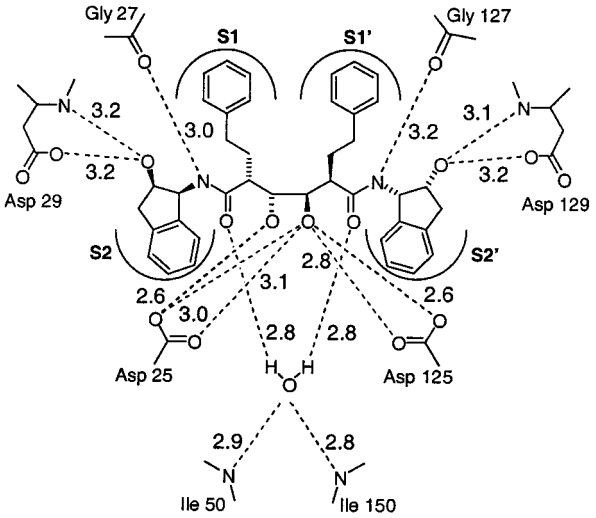


Figure 5. Schematic drawing of inhibitor **8b** complexed with HIV-1 PR. Interatomic distances for possible hydrogen bonds are shown in Å.

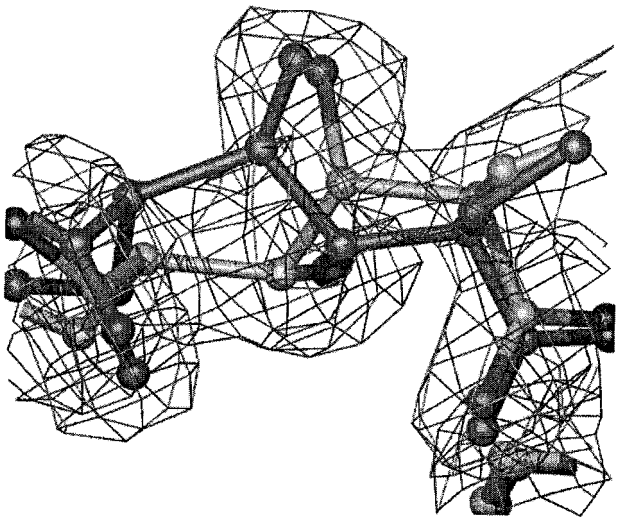


Figure 6. $F_o - F_c$ inhibitor-omit electron density map for **8b** contoured at 1σ, showing the superimposition of the central diol of **8b** (light) and **6** (dark). The inversion of configuration of inhibitor **8b** in contrast to inhibitor **6** was confirmed in the electron density map. The image has been compiled using the protein modeling software O[49] and the web-based imaging program MOLRAY.[50]

contrast, optimal distances were observed for inhibitor **6** (2.73 and 2.78 Å, respectively). Replacing the *O*-benzylated P1/P1′ substituents of inhibitor **6** with phenethyl ($-CH_2CH_2Ph$) P1/P1′ substituents as in inhibitor **8b** adds different angular restraints between the atoms. This is observed in the structure as an orientation change of the P1/P1′ substituents of **8b** compared to **6** (Figure 7). The ether oxygen of inhibitor **6** can in theory act as a hydrogen-bond acceptor. However, its closest neighbor, WAT307, is not in range for hydrogen-bond formation (4.8 Å). Hence, a methylene group in that position does not reduce binding as a consequence of fewer interactions. More likely the hydrophobic contribution of the methylene group has positive effects on binding to the highly lipophilic S1/S1′ subsites. The positioning of the P1′ substituent of **8b** is also affected by the configuration change of the stereogenic centers carrying the central diol. As opposed

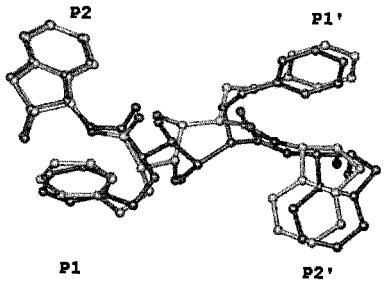


Figure 7. Conformational comparison of inhibitors **6** (dark) and **8b** (light) when bound to the HIV-1 PR active site. The difference in configuration of stereogenic centers carrying the central diol affects the positioning of the P1′ and P2′ substituents into respective subsites. Consequently, when comparing the positioning of the P1′/P2′ substituents of **8b** and **6**, P1′ of **8a** and P2′ of **6** reach deeper into respective subsites (0.3 and 0.8 Å, respectively). The image has been compiled using the protein modeling software O[49] and the web-based imaging program MOLRAY.[50]

to the P2′ substituent, the P1′ substituent is positioned 0.3 Å deeper in the S1′ subsite compared to the P1′ substituent of **6** (Figure 7). As a consequence of close-packing interactions to the P2/P2′ substituent and S1/S1′ subsites, the phenyl rings are held coplanar for both inhibitors. In conclusion, the exchange of the ether oxygen for a methylene group in the P1/P1′ substituents induces minor orientational and positional shifts with negligible effects on binding efficacy to the S1/S1′ subsites. The configuration of the central diol in inhibitor **8b** is confirmed to be (*R*,*R*), consequently compound **21c** is the (*S*,*S*)-diol and inhibitor **9b** is the (*R*,*R*)-diol.

Conclusion

The present carba analogues of inhibitor **6** show a novel SAR pattern relating to the diol stereochemistry. This highlights the importance of validating optimal diol stereochemistry, by synthesis and screening, while C_2-symmetric inhibitors are optimized. A very promising feature of the potent inhibitor **8b** is that although it is more lipophilic and less potent than inhibitor **6**, it shows better antiviral activity in the presence of 40% human serum (ED_{50}+40% hs = 0.39 μM, cf. ED_{50}+50% hs = 1.5 μM for inhibitor **6**), a screening parameter important for clinical efficacy. The preparation of the corresponding (*S*,*S*)-diol is currently being investigated by an alternative synthetic route.

Experimental Section

Crystallography. The details of the crystallization and structure determination will be published elsewhere. Briefly, the complex of HIV-1 PR and **8b** was crystallized in space group $P2_12_12$ and determined to 2.0 Å resolution with an *R*-value of 0.21 (R_{free} 0.24).

HIV-1 Protease Inhibition (Table 1, Column 2). HIV-1 protease was cloned and heterologously expressed in *Escherichia coli*,[51] and K_i values were determined using a fluorometric assay.[52]

In Vitro Anti-HIV Activity (Table 1, Column 3). The anti-HIV activity was measured in a HIV cytopathic assay in MT-4 cells, where the effect was quantified using vital dye XTT.[53] The 50% inhibitory concentrations (ED_{50}) were calculated from the percent cytoprotection for individual compounds.

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 and/or treatment with ninhydrin in ethanol. 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. Unless stated otherwise, all materials were obtained from commercial suppliers and used without further purification. Yields are not optimized.

(4*R*,5*S*)-Indano[1,2-*d*]oxazolidin-2-one (11). (1*R*,2*S*)-1-Amino-2-indanol (18.4 g, 0.125 mol) was dissolved in CH_2Cl_2 (1350 mL) under a nitrogen atmosphere. The temperature was lowered to 0 °C before addition of triphosgene (14.8 g, 49.9 mmol, 0.4 equiv) and NEt_3 (35.0 mL, 0.251 mol, 2.0 equiv). Stirring was continued at 0 °C for 1.5 h, when TLC (R_f 0.39, $CHCl_3$–MeOH 15:1) showed completion of the reaction. The mixture was concentrated to 675 mL and washed with NH_4Cl (1×) and H_2O (2×) and the combined aqueous layers were extracted with EtOAc (2×). The organic layers were combined with the mixture from above, dried ($MgSO_4$), and concentrated to give **11** (20.9 g, 0.119 mol, 95%) as white crystals: $[\alpha]^{20}_D$ +71 (*c* 0.65, EtOAc); mp 200−201 °C; ^1H NMR (300 MHz, $CDCl_3$ and CD_3OD) δ 3.32 (dd, 1 H, J = 1.76, 18.0 Hz), 3.43 (dd, 1 H, J = 6.15, 18.0 Hz), 3.74 (s, 1 H), 5.18 (d, 1 H, J = 7.47 Hz), and 5.42 (ddd, 1 H, J = 1.76, 6.15, 7.47 Hz); ^{13}C NMR (67 MHz, $CDCl_3$ and CD_3OD) δ 38.5, 61.0, 80.5, 124.6, 125.3, 127.6, 129.1, 139.5, 140.1, and 159.9. Anal. ($C_{10}H_9NO_2$) C, H, N.

***N*-(4-Phenylbutyryl)-(4*R*,5*S*)-indano[1,2-*d*]oxazolidin-2-one (12).** To a stirred solution of 4-phenylbutyric acid **10** (35.0 g, 0.214 mol) and $SOCl_2$ (98 mL, 1.34 mol, 6.3 equiv) was added pyridine (0.64 mL, 7.9 mmol, 0.04 equiv). The solution was stirred at room temperature for 30 min and at 40 °C for an additional 1 h before it was concentrated to give 4-phenylbutanoyl chloride (38.3 g, 0.210 mol, 98%) as a yellow oil, which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (dt, 2 H, J = 7.6, 7.3 Hz), 2.67 (t, 2 H, J = 7.6 Hz), 2.88 (t, 2 H, J = 7.3 Hz), and 7.15−7.32 (m, 5 H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 26.4, 34.0, 46.1, 126.2, 128.3, 128.4, 140.2, and 173.4.

NaH (1.61 g, 67.1 mmol, 1.1 equiv) was suspended in DMF (150 mL) under an argon atmosphere and the temperature was lowered to 0 °C. A dropping funnel was charged with the chiral auxiliary **11** (10.7 g, 61.2 mmol) in DMF (90 mL), a second dropping funnel was charged with 4-phenylbutanoyl chloride (13.4 g, 73.4 mmol, 1.2 equiv) in DMF (90 mL), and the two solutions were then added simultaneously to the stirred NaH suspension during 30 min. Stirring was continued at 0 °C for an additional 3 h (R_f 0.56, toluene−EtOAc 10:1), before slow addition of MeOH and H_2O. The layers were separated after dilution with toluene and H_2O. The organic layer was washed with H_2O (2x), followed by extraction of the combined aqueous layers with toluene (1×). Finally, the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (toluene; toluene−EtOAc 40:1) gave **12** (14.3 g, 44.5 mmol, 73%) as a colorless syrup: $[\alpha]^{20}_D$ −209 (*c* 0.948, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.98−2.08 (m, 2 H), 2.70 (t, 2 H, J = 7.69 Hz), 3.00 (ddd, 2 H, J = 1.76, 7.47, 9.23 Hz), 3.37 (d, 2 H, J = 3.52 Hz), 5.26 (ddd, 1 H, J = 3.08, 4.40, 7.47 Hz), 5.91 (d, 1 H, J = 7.03 Hz), 7.16−7.37 (m, 8 H), and 7.62 (d, 1 H, J = 7.03 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 26.0, 34.8, 35.2, 38.0, 63.0, 78.0, 125.2, 126.0, 127.2, 128.2, 128.4, 128.5, 129.8, 139.2, 139.5, 141.6, 153.0, and 173.4. Anal. ($C_{20}H_{19}NO_3$) C, H, N.

***N*-[(2*S*)-2-(Hydroxymethyl)-4-phenylbutyryl]-(4*R*,5*S*)-indano[1,2-*d*]oxazolidin-2-one (13).** $TiCl_4$ (3.6 mL, 32.8 mmol, 1.05 equiv) was added to a stirred solution of compound **12** (10.0 g, 31.1 mmol) in CH_2Cl_2 (525 mL), under an argon atmosphere, with the temperature kept at 0 °C. A yellow precipitate was formed within 30 min, DIEA (5.5 mL, 31.9 mmol, 1.0 equiv) was added (the color changed from yellow to red), and stirring was continued at 0 °C for 1 h. Trioxane (2.08 g, 23.1 mmol, 0.74 equiv) and $TiCl_4$ (4.5 mL, 40.9 mmol, 1.3 equiv) were added, and stirring was continued until TLC (R_f 0.15, toluene−EtOAc 10:1) showed complete reaction (3 h). During this time the color of the reaction changed from dark red to light brown. Neutralization (pH = 7) of the cold reaction was performed by adding saturated aqueous $NaHCO_3$ (500 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was immediately purified using column chromatography (toluene; toluene−EtOAc 10:1) to give alcohol **13** (8.1 g, 23.0 mmol, 74%) as a colorless syrup, which solidified upon standing: $[\alpha]^{20}_D$ −174 (*c* 1.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 1 H), 1.90−2.02 (m, 1 H), 2.15−2.24 (m, 1 H), 2.63−2.84 (m, 2 H), 3.36 (d, 2 H, J = 3.52 Hz), 3.84 (m, 2 H), 3.94−4.02 (m, 1 H), 5.14−5.19 (m, 1 H), 5.72 (d, 1 H, J = 7.03 Hz), 7.18−7.36 (m, 8 H), and 7.58 (d, 1 H, J = 7.47 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 29.9, 33.8, 37.7, 45.2, 63.2, 63.8, 78.2, 125.1, 126.0, 127.1, 128.2, 128.3, 128.6, 129.8, 138.9, 139.3, 141.2, 152.9, and 175.9. Anal. ($C_{21}H_{21}NO_4$) C, H, N.

***N*-[(2*S*)-2-(Benzyloxymethyl)-4-phenylbutyryl]-(4*R*,5*S*)-indano[1,2-*d*]oxazolidin-2-one (14).** To a stirred solution of alcohol **13** (18.2 g, 51.7 mmol) and benzyl 2,2,2-trichloroacetimidate (11.6 mL, 62.4 mmol, 1.2 equiv) in 1,4-dioxane (900 mL) was added TMS−OTf (0.9 mL, 4.96 mmol, 0.1 equiv) dropwise under argon. Within 1 h the color changed to brown-yellow and TLC (R_f 0.47, toluene−EtOAc 10:1) showed completion of the reaction. The reaction mixture was filtered through a pad of SiO_2/$NaHCO_3$/SiO_2 in a glass filter-funnel and concentrated. Purification by column chromatography (toluene−EtOAc 40:1) gave the benzylated compound **14** (20.2 g, 45.8 mmol, 89%) as a colorless syrup: $[\alpha]^{20}_D$ −117 (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.87−1.98 (m, 1H), 2.15−2.27 (m, 1 H), 2.61−2.78 (m, 2 H), 3.35 (d, 2 H, J = 3.08 Hz), 3.64 (dd, 1 H, J = 5.27, 9.22 Hz), 3.78 (dd, 1 H, J = 7.03, 9.22 Hz) 4.23 (m, 1 H), 4.41 (s, 2 H), 5.13−5.17 (m, 1 H), 5.78 (d, 1 H, J = 7.03 Hz), 7.11−7.47 (m, 14 H), and 7.55 (d, 1 H, J = 7.91 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 30.3, 33.7, 37.8, 43.2, 63.0, 71.2, 72.9, 77.8, 125.0, 126.0, 127.2, 127.3, 128.0, 128.2, 128.3, 128.6, 129.7, 138.1, 139.1, 139.3, 141.4, 152.6, and 174.8. Anal. ($C_{28}H_{27}NO_4$) C, H, N.

(2*R*)-2-(Benzyloxymethyl)-4-phenyl-1-butanol (15). The benzylated compound **14** (3.85 g, 8.72 mmol) was dissolved in THF (90 mL) under an argon atmosphere, the temperature was lowered to −60 °C, and LAH (3.38 g, 89.0 mmol, 10 equiv) was added. Stirring was continued at −60 °C for 30 min and at 0 °C for 1 h (R_f 0.2, toluene−EtOAc 9:1). The reaction mixture was acidified by the addition of cold 0.6 M HCl. The suspension was extracted with Et_2O (5×), and the combined organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (toluene−EtOAc 3:1) gave alcohol **15** (1.96 g, 7.25 mmol, 83%) as a colorless oil: $[\alpha]^{20}_D$ +14 (*c* 0.90, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.57−1.71 (m, 2 H), 1.86−1.93 (m, 1 H), 2.49 (s, 1 H), 2.57−2.67 (m, 2 H), 3.50−3.53 (m, 1 H), 3.62−3.69 (m, 2 H), 3.74−3.78 (m, 1 H), 4.51 (q, 2 H, J = 12.1 and 17.6 Hz), and 7.15−7.36 (m, 10 H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 29.8, 33.3, 40.1, 65.5, 73.4, 125.8, 127.6, 127.7, 128.3, 128.4, 138.0, and 142.1. Anal. ($C_{18}H_{22}O_2$) C, H.

(2*S*)-2-[(Benzyloxymethyl)-4-phenylbutyl] (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. The Mosher's ester of alcohol **15** was prepared according to the method described by Wipf and Fritch,[34] using 26 mg (0.096 mmol) of **15** in 1.4 mL of CH_2Cl_2 together with 580 μL of pyridine and 210 μL of (*S*)−(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride with stirring during 40 min. Purification by column chromatography (toluene−EtOAc 40:1) gave the ester (38 mg, 0.078 mmol, 81%) as an oil: ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 33.1, 37.8, 55.4, 66.4, 69.6, 73.2, 121.3, 125.2, 125.8, 127.2, 127.4, 127.5, 128.2, 128.3, 129.5, 132.2, 138.1, 141.5, and 166.4.

2-[(Benzyloxymethyl)-4-phenylbutyl] (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. The racemic alcohol **15** was prepared by monobenzylation of 2-phenethylpropane-1,3-diol[54] (1.0 equiv) using NaH (1.02 equiv) and BnBr

(1.02 equiv) in DMF under an atmosphere of nitrogen (0 °C to room temperature, 2 h), which after column chromatography produced a 62% yield of racemic alcohol **15** as a transparent syrup. The Mosher's ester of racemic **15** was prepared as described above using 20 mg (0.074 mmol) of racemic **15**, which gave the racemic ester (28 mg, 0.058 mmol, 78%) as an oil: ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8, 29.9, 33.0, 37.8 (2 C), 55.4, 66.2, 66.4, 69.6, 69.7, 73.2, 121.4, 125.2, 125.8, 127.2, 127.4 (2 C), 127.5, 128.2, 128.3, 129.5, 138.1, and 141.5.

(2*S*)-2-(Benzyloxymethyl)-4-phenylbutanal (16). DMSO (4.03 mL, 56.7 mmol, 2.2 equiv) in CH_2Cl_2 (11.3 mL) was added to a solution of oxalyl chloride (2.43 mL, 28.3 mmol, 1.1 equiv) in CH_2Cl_2 (64 mL) at −70 °C under argon. After stirring for 5 min, alcohol **15** (6.97 g, 25.8 mmol) dissolved in CH_2Cl_2 (26 mL) was added dropwise (20 min). Stirring was continued for an additional 20 min. NEt_3 (7.18 mL, 54.0 mmol, 2.1 equiv) was added, and the reaction mixture was stirred during 5 min at −70 °C and subsequently during 1 h while the reaction mixture slowly was allowed to attain room temperature (R_f 0.35, pentane−EtOAc 15:1 and R_f 0.57, toluene−EtOAc 9:1). Dilution with H_2O, extraction of the aqueous layer with CH_2Cl_2 (3×), drying ($MgSO_4$), and concentration gave the crude aldehyde **16**. Purification by column chromatography (pentane−EtOAc 25:1; 15:1 and 10:1) gave **16** (5.64 g, 21.0 mmol, 82%) as a transparent oil, which was used immediately in the next step: $[\alpha]^{20}_D$ +17 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72−1.86 (m, 1 H), 1.97−2.12 (m, 1 H), 2.48−2.58 (m, 1 H), 2.62 (t, 2 H, J = 7.97 Hz), 3.67 (d, 2 H, J = 5.50 Hz), 4.47 (d, 2 H, J = 1.65 Hz), 7.12−7.40 (m, 10 H), and 9.68 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3, 32.9, 51.3, 68.3, 73.1, 125.8, 127.4, 127.5, 128.1, 128.2 (2 C), 137.6, 140.9, and 203.1. Anal. ($C_{18}H_{20}O_2 \cdot {}^1/_2H_2O$) C, H.

Reduction of Aldehyde 16 with Borane−Dimethyl Sulfide Complex (BMS). Aldehyde **16** was reduced with BMS according to the method described by Brown et al.,[55] using 64 mg (0.238 mmol) of **16** in 2.0 mL of Et_2O together with 60 μL of BMS with stirring at 0 °C during 30 min, followed by stirring at room temperature during 2.5 h. Purification by column chromatography (toluene−EtOAc 3:1) gave alcohol **15** (50 mg, 0.185 mmol, 78%) as an oil. Alcohol **15** (20 mg, 0.074 mmol) was converted to the Mosher's ester (28 mg, 0.058 mmol, 78%) according to the method described above. ^{13}C NMR spectral data were in agreement with those reported above for (2*S*)-2-[(benzyloxymethyl)-4-phenylbutyl] (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate.

(2*S*)-2-{(4*R*,5*S*)-5-[(1*S*)-1-(Hydroxymethyl)-3-phenylpropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-4-phenyl-1-butanol (19a), (2*S*)-2-{(4*R*,5*R*)-5-[(1*S*)-1-(Hydroxymethyl)-3-phenylpropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-4-phenyl-1-butanol (19b), and (2*S*)-2-{(4*R*,5*R*)-5-[(1*S*)-1-(Hydroxymethyl)-3-phenylpropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-4-phenyl-1-butanol (19c). Zinc dust (prewashed with 1 M HCl, EtOH, acetone, and CH_2Cl_2) (2.72 g, 41.6 mg-atom, 2.0 equiv) was added to a solution of VCl_3 $(THF)_3$ in CH_2Cl_2 (50 mL, 0.5 M, 25 mmol, 1.2 equiv), under an argon atmosphere, changing the color of the solution from deep-red to violet. The mixture was stirred at room temperature during 80 min, while the color slowly changed from violet to black-green. DMI (16.0 mL, 146 mmol, 7.0 equiv) was added, and stirring was continued during 15 min, before dropwise addition (40 min) of aldehyde **16** (5.59 g, 20.8 mmol) dissolved in CH_2Cl_2 (56 mL), which gave a brown reaction mixture. The reaction was quenched after 20 h (R_f **17a** 0.32 and R_f **17b**, **17c** 0.21, toluene−EtOAc 9:1), by the addition of 1 M HCl (127 mL). Stirring of the two-phase mixture during 30 min gave a turquoise aqueous layer and a brown organic layer, which were separated. Additional extraction of the aqueous layer with CH_2Cl_2 (3×), drying ($MgSO_4$), concentration, and subsequent separation by column chromatography (toluene; toluene−EtOAc 25:1 and 15:1) gave **17a** (2.29 g) and a mixture of **17b** and **17c** (2.16 g), all of which were used in the next step without further purification.

(17a): ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 31.3, 33.8, 34.0, 38.4, 39.8, 70.2, 72.9, 73.5, 73.6 (2 C), 75.9, 125.6, 127.5, 127.7, 127.8, 128.1, 128.2 (2 C), 128.3 (2 C), 137.4, 137.7, 142.2, and 142.4.

(17b and **17c):** ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 31.1, 33.5, 33.8, 40.7 (2 C), 70.3, 70.4, 72.6, 73.4, 73.7, 73.9, 125.7 (2 C), 127.5, 127.6 (2 C), 127.7, 128.2 (2 C), 128.3 (2 C), 137.7, 142.2, and 142.1.

Step II. Isopropylidene Protection. 2,2-Dimethoxypropane (2.5 equiv) and CSA (0.8 equiv) were added to a solution of **17a**−**c** (1.0 equiv) in acetone (5.3 mL/mmol) under nitrogen. After stirring for 30 min, when TLC (R_f **18a** 0.63 and R_f **18b**,**18 c** 0.72, toluene−EtOAc 9:1) showed completion of the reaction, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc (3×). Activated charcoal and Na_2SO_4 were added to the organic layer, which was stirred for 10 min before filtration through a pad of Celite and Na_2SO_4 and concentration. Column chromatography (toluene; toluene−EtOAc 20:1 and 9:1) gave the crude product, which was used in the next step without further purification.

18a. The isopropylidene-protected compound was prepared according to step II, using 2.29 g of **17a**, and isolated as a white solid (2.29 g): ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 26.2, 29.6, 31.0, 33.0, 33.3, 38.0, 38.2, 69.6, 71.1, 73.0, 73.1, 77.1, 77.5, 106.9, 125.6 (2 C), 127.3 (2 C), 127.4, 128.1, 128.2 (3 C), 128.3, 128.4, 138.5, 138.8, 142.3, and 142.4.

18b and **18c.** The isopropylidene-protected compounds was prepared according to step II, using 2.16 g of the mixture **17b** and **17c**, and isolated a transparent syrup (1.95 g). After column chromatography a small amount of alcohol **15** (265 mg, 0.980 mmol) was isolated as well. ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4, 28.6, 31.5, 33.4, 33.8, 40.2, 40.7, 69.4, 70.7, 72.9, 73.0, 79.1, 79.3, 107.5, 107.8, 125.6, 125.7, 127.3 (2 C), 127.5, 128.1, 128.2 (2 C), 128.3, 138.4 (2 C), 142.2, and 142.3.

Step III. Debenzylation. Compounds **18a**−**c** (1.0 equiv) were dissolved in EtOAc (23 mL/mmol) and $NaHCO_3$ (3.0 equiv), a minor amount of H_2O and Pd/C (0.8 g) was added. The suspension was stirred at room temperature under a hydrogen atmosphere. After 19, 39, and 47 h, the suspension was filtered through a pad of Celite and Na_2SO_4, fresh reagents were added, and stirring under hydrogen was continued. When TLC showed completion of the reaction (R_f **19a** 0.33, R_f **19b**, **19c** 0.31, toluene−EtOAc 1:1) after 63 h, filtration and concentration followed by column chromatography (toluene−EtOAc 2:1) gave compounds **19a**−**c**.

19a. The title compound was prepared according to step III, using 2.47 g of **18a**, and isolated as a transparent syrup (1.27 g, 3.19 mmol): $[\alpha]^{20}_D$ +91 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3 H), 1.37 (s, 3 H), 1.59−1.71 (m, 4 H), 1.90 (s, 1 H), 1.97 (s, 1H), 2.12−2.28 (m, 3 H), 2.49−2.67 (m, 3 H), 3.57−3.77 (m, 4 H), 4.03−4.08 (m, 1 H), 4.29−4.32 (dd, 1 H, J = 2.64, 6.59 Hz), and 7.03−7.25 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 26.1, 27.3, 30.4, 32.8, 33.1, 38.6, 39.5, 64.0, 64.2, 79.2, 81.0, 108.1, 125.8, 126.0, 128.3 (2 C), 128.4, 128.5, 141.4, and 141.9. Anal. ($C_{25}H_{34}O_4 \cdot {}^1/_4H_2O$) C, H.

19b and **19c.** The mixture of the title compounds was prepared according to step III, using 1.77 g of the mixture of **18b** and **18c**, and isolated as a transparent syrup (1.03 g, 2.58 mmol): ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 27.1, 27.3, 30.6, 33.3, 33.5, 40.6, 41.1, 62.2, 63.4, 79.9, 81.9, 108.8, 108.3, 125.8 (2 C), 128.2 (2 C), 128.3, 141.5, and 141.8. Anal. ($C_{25}H_{34}O_4 \cdot {}^1/_3H_2O$) C, H.

Diol **19a** and the mixture of diols **19b** and **19c** were isolated with a total yield of 64% over three steps (2.30 g 5.77 mmol). A small amount of alcohol **15** (265 mg, 0.980 mmol) was also isolated.

General Method for the Preparation of Compounds 20a−c. Method I. The diols **19a**−**c** (1.0 equiv) were dissolved in a stirred mixture of CH_3CN (4 mL/mmol), CH_2Cl_2 (4 mL/mmol), and H_2O (6 mL/mmol). $RuCl_3 \cdot xH_2O$ (0.05 equiv) and $NaIO_4$ (9.0 equiv) were added. TLC (toluene−EtOAc 1:3) showed completion of the reaction after vigorous stirring for 105 min. The reaction mixture was diluted with CH_2Cl_2 (1 vol) and stirred for an additional 10 min. Water was added (1 vol) and the aqueous layer was extracted with EtOAc (4×). The combined organic layers were dried ($MgSO_4$) and concentrated

to provide the corresponding carboxylic acid, which was immediately activated without further purification.

A mixture of the carboxylic acid, DSC (5.0 equiv), and pyridine (6.9 equiv) in CH_3CN (16 mL/mmol) was stirred under an argon atmosphere. When TLC showed completion of the reaction after 23 h (R_f **20a** 0.63, R_f **20b** 0.47 and R_f **20c** 0.58, toluene−EtOAc 1:1), toluene (0.5 vol) was added and the reaction mixture was concentrated. The residue was dissolved in EtOAc and extracted with water (5×), and the combined aqueous layers were washed with EtOAc (3×). The combined organic layers were dried (Na_2SO_4), concentrated, and purificated by column chromatography (toluene−EtOAc 4:1) to provide the disuccinimidyl esters **20a**−**c**.

Succinimidyl (2*R*)-2-[(4*R*,5*S*)-5-(3-Phenylpropyl-(1*R*)-1-succinimidyloxycarbonyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-phenylbutanoate (20a). The title compound was prepared according to method I, using 1.14 g (2.87 mmol) of diol **19a**, and isolated as a white foam in 22% yield (393 mg, 0.633 mmol): $[\alpha]^{20}_D$ +19 (*c* 0.35, $CDCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.7, 26.8, 31.8, 32.0, 32.5, 32.6, 42.2, 43.5, 76.0, 77.8, 108.9, 125.2, 125.9 (2 C), 128.1, 128.2, 128.3, 128.5, 128.7, 128.9, 140.9, 141.1, 168.2, 168.5, 168.6, and 168.8. Anal. ($C_{33}H_{36}N_2O_{10}$) C, H, N.

Succinimidyl (2*R*)-2-[(4*R*,5*R*)-5-(3-Phenylpropyl-(1*R*)-1-succinimidyloxycarbonyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-phenylbutanoate (20b) and Succinimidyl (2*R*)-2- [(4*S*,5*S*)-5-(3-phenylpropyl-(1*R*)-1-succinimidyl-oxycarbonyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-phenyl-butanoate (20c). The title compounds, separated by column chromatography, were prepared according to method I, using 965 mg (2.42 mmol) of the mixture of diols **19b** and **19c**, and isolated as white foams in 43% total yield (**20b**, 126 mg, 0.203 mmol; **20c**, 527 mg, 0.849 mmol).

(20b): $[\alpha]^{20}_D$ +86 (*c* 0.40, $CDCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 27.4, 29.8, 32.7, 45.6, 78.8, 110.4, 126.0, 128.1, 128.3, 128.6, 128.9, 140.8, 168.3, and 168.5. Anal. ($C_{33}H_{36}N_2O_{10}\cdot{}^1/_4H_2O$) C, H, N.

(20c): $[\alpha]^{20}_D$ −5.3 (*c* 0.75, $CDCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 27.6, 27.9, 31.4, 31.7, 32.6, 33.0, 45.0, 78.5, 80.2, 110.3, 125.2, 125.9, 126.1, 128.1, 128.3, 128.4, 128.6, 128.9, 140.4, 167.5, and 168.6. Anal. ($C_{33}H_{36}N_2O_{10}$) C, H, N.

General Method for the Preparation of Compounds 8a and 8b. Method II. The disuccinimidyl esters **20a**−**c** (1.0 equiv) and (1*S*,2*R*)-1-amino-2-indanol (6.3 equiv) were dissolved in DCE (30 mL/mmol) under a nitrogen atmosphere. The reaction was stirred at 60 °C until TLC (R_f **21a** 0.31, R_f **21b** 0.43 and R_f **21c** 0.19, toluene−EtOAc 1:1) showed completion of the reaction (16−20 h). Concentration followed by column chromatography (toluene−EtOAc 3:1 and 1:1) gave the amides **21a**−**c**.

A mixture of $FeCl_3\cdot 6H_2O$ (3.5 equiv) and the amides **21a** and **21b** (1.0 equiv) were dissolved in warm CH_2Cl_2 (15 mL/mmol) and stirred at room temperature for 1 and 8 h, respectively; for compound **21b**, the reaction was concentrated and new CH_2Cl_2 was added every other hour (R_f **8a** 0.18, R_f **8b** 0.21, $CHCl_3$–MeOH 20:1). Saturated aqueous $NaHCO_3$ (1 vol) was added and the aqueous layer was extracted with CH_2Cl_2 (3×) and EtOAc (3×). Drying ($MgSO_4$), concentration, and purification by column chromatography ($CHCl_3$; $CHCl_3$−MeOH 40:1 and 30:1), followed by trituration from EtOAc, gave the target compounds **8a** and **8b**.

21a: ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 25.4, 32.7, 32.9, 33.4, 34.0, 39.2, 39.7, 46.1, 46.7, 58.0, 58.2, 73.4, 73.6, 77.4, 77.7, 107.5, 123.6, 125.0, 125.3, 125.4, 125.9, 126.0, 126.8, 127.1, 128.1, 128.3 (2 C), 128.4, 128.6, 139.8, 140.1, 140.4, 141.1, 141.5, 173.2, and 174.7.

21b: ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3, 29.6, 33.4, 39.5, 49.8, 57.7, 73.5, 79.6, 108.9, 124.7, 125.2, 126.0, 127.2, 128.3, 128.5, 140.0, 140.2, 141.0, and 172.9.

21c: 29% yield (73 mg, 0.106 mmol); $[\alpha]^{20}_D$ +15 (*c* 0.48, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$ and CD_3OD) δ 1.40 (s, 6H), 1.77−1.84 (m, 2 H), 2.00−2.10 (m, 2 H), 2.60−2.68 (m, 4 H), 2.74−2.82 (m, 2 H), 2.96 (d, 2 H, J = 16.41 Hz), 3.17 (dd, 2 H, J = 4.69, 16.02 Hz), 3.67 (d, 2 H, J = 3.12 Hz), 4.17 (d, 2 H, J = 5.86 Hz), 4.61−4.64 (m, 2 H), 5.42 (d, 2 H, J = 5.08 Hz), and 7.15−7.35 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$ and CD_3OD) δ 26.9, 31.5, 33.1, 39.6, 50.6, 57.2, 72.5, 79.7, 108.9, 124.0, 124.9, 125.7, 126.5, 127.7, 128.0, 128.1, 139.9, 140.4, 140.7, and 173.2. Anal. ($C_{43}H_{48}N_2O_6\cdot H_2O$) C, H, N.

***N*^{1},*N*^{6}-Bis[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-2,5-bis(2-phenylethyl)hexanediamide (8a).** The title compound was prepared according to method II, using 195 mg (0.314 mmol) of the disuccinimidyl ester **20a**, and isolated as a white solid in 47% yield (96 mg, 0.148 mmol): $[\alpha]^{20}_D$ +20 (*c* 0.94, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$ and CD_3OD) δ 1.97−2.23 (m, 4 H), 2.61−2.85 (m, 6 H), 2.92−2.99 (m, 2 H), 3.12−3.19 (m, 2 H), 3.69 (bs, 1 H), 3.91−3.94 (m, 1 H), 4.48 (s, 6 H), 4.54−4.61 (m, 2 H), 5.38−5.41 (m, 2 H), and 7.13−7.30 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$ and CD_3OD) δ 33.3 (2 C), 39.3, 47.0, 56.8, 56.9, 72.3, 72.4, 72.7, 73.4, 123.6, 123.8, 124.7, 125.3, 125.4, 126.5, 127.5, 127.8 (3 C), 139.7, 139.8, 140.2, 141.1, 141.5, and 175.9. Anal. ($C_{40}H_{44}N_2O_6\cdot{}^1/_2H_2O$) C, H, N.

***N*^{1},*N*^{6}-Bis[(2*R*)-hydroxy-(1*S*)-indanyl]-(2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-bis(2-phenylethyl)hexanediamide (8b).** The title compound was prepared according to method II, using 67 mg (0.108 mmol) of the disuccinimidyl ester **20c**, and isolated as a white solid in 58% yield (41 mg, 0.063 mmol): $[\alpha]^{20}_D$ +30 (*c* 0.77, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$ and CD_3OD) δ 1.99−2.03 (m, 2 H), 2.05−2.15 (m, 2 H), 2.60−2.69 (m, 4 H), 2.76−2.84 (m, 2 H), 2.95 (dd, 2 H, J = 2.20, 16.48 Hz), 3.15 (dd, 2 H, J = 5.13, 16.48 Hz), 3.81 (d, 2 H, J = 8.79 Hz), 4.24 (s, 6 H), 4.60−4.63 (m, 2 H), 5.41 (d, 2 H, J = 5.13 Hz), and 7.16−7.33 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$ and CD_3OD) δ 30.8, 33.4, 39.4, 50.8, 57.1, 71.6, 72.6, 124.0, 124.7, 125.5, 126.6, 127.6, 127.9, 139.8, 140.0, 141.2, and 174.6. Anal. ($C_{40}H_{44}N_2O_6\cdot H_2O$) C, H, N.

General Method for the Preparation of Compounds 9a and 9b. Method III. The disuccinimidyl esters **20 a**−**c** (1.0 equiv) and H-Val-NHMe (6.3 equiv) were dissolved in DCE (30 mL/mmol) under a nitrogen atmosphere. The reaction was stirred at 50 °C until TLC (R_f **23a** 0.34, R_f **23b** 0.41, $CHCl_3$−MeOH 9:1) showed completion of the reaction (22 h). Concentration followed by column chromatography ($CHCl_3$−MeOH 20:1) gave the amides **23a** and **23b**.

A mixture of $FeCl_3\cdot 6H_2O$ (3.5 equiv) and the amides **23a** and **23b** (1.0 equiv) was dissolved in warm CH_2Cl_2 (17.5 mL/mmol) and stirred at room temperature. The reaction was followed with TLC (R_f **9a** 0.23, R_f **9b** 0.40, $CHCl_3$−MeOH 9:1), and every other hour the reaction was concentrated and new CH_2Cl_2 was added. When TLC showed completion of the reaction (**9a**, 4 h and **9b**, 8 h) saturated aqueous $NaHCO_3$ (1 vol) was added and the aqueous layer was extracted with CH_2Cl_2 (3×) and EtOAc (3×). Drying ($MgSO_4$), concentration, and purification by column chromatography ($CHCl_3$; $CHCl_3$−MeOH 30:1 and 20:1), followed by trituration from EtOAc, gave the target compounds **9a** and **9b**.

23a: ^{13}C NMR (75 MHz, $CDCl_3$ and CD_3OD) δ 19.0, 24.3, 25.6, 25.7, 25.8, 30.8, 31.0, 31.6, 32.0, 32.3, 33.0, 46.1, 46.5, 58.5, 59.0, 76.4, 77.9, 107.7, 125.8, 128.0, 128.2, 140.9, 141.6, 172.1, 172.2, 173.0, and 174.0.

23b: ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 19.5, 26.2, 27.2, 29.7, 30.6, 33.6, 49.1, 58.8, 79.1, 109.1, 125.9, 128.3, 141.2, 171.6, and 172.6.

***N*^{1},*N*^{6}-Bis[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-2,5-bis(2-phenylethyl)hexanediamide (9a).** The title compound was prepared according to method III, using 153 mg (0.247 mmol) of the disuccinimidyl ester **20b**, and isolated as a white solid in 7% yield (10 mg, 0.017 mmol) together with recovered **23a** (26 mg, 0.040 mmol): $[\alpha]^{20}_D$ −27 (*c* 0.32, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$ and CD_3OD) δ 0.92 (d, 3 H, J = 6.64 Hz), 0.97 (d, 9 H, J = 6.64 Hz), 1.85−2.19 (m, 6 H), 2.54−2.72 (m, 6 H), 2.76 (s, 3 H), 2.77 (s, 3 H), 3.60−3.62 (m, 1 H), 3.70−3.73 (m, 1 H), 4.12−4.18 (m, 2 H), 4.56 (s, 6 H), and 7.16−7.55 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$ and CD_3OD) δ 17.8, 18.7, 18.8, 25.2, 28.4, 30.1, 30.3, 32.5, 33.2, 46.5, 58.3, 58.5, 72.5, 73.5, 125.2, 125.3, 127.6, 127.7, 127.8, 141.0, 141.3, 171.8, 171.9,

175.2, and 175.4. HRMS calcd for $C_{34}H_{50}O_6N_4$ [M + Na] 633.3628, found [M + Na] 633.3604.

***N*¹,*N*⁶-Bis[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-bis(2-phenylethyl)hexanediamide (9b).** The title compound was prepared according to method III, using 52 mg (0.084 mmol) of the disuccinimidyl ester **20b**, and isolated as a white solid in 22% yield (11 mg, 0.018 mmol) together with recovered **23b** (16 mg, 0.025 mmol): $[\alpha]^{20}_D$ −23 (*c* 0.75, $CHCl_3$−MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$ and CD_3OD) δ 0.60−0.64 (m, 12 H), 1.61−1.74 (m, 6 H), 2.18−2.26 (m, 6 H), 2.42 (s, 6 H), 3.34 (d, 2 H, J = 8.59 Hz), 3.76−3.78 (m, 2 H), 4.32 (s, 6 H), and 6.81−7.27 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$ and CD_3OD) δ 17.8, 18.5, 25.1, 29.9, 30.8, 33.0, 50.4, 58.7, 71.1, 125.1, 127.5, 141.0, 171.9, and 174.1. HRMS calcd for $C_{34}H_{50}O_6N_4$ [M + Na] 633.3628, found [M + Na] 633.3638.

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