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An Efficient Synthesis of a Hydroxyethylamine (HEA) Isostere and Its α-Aminophosphonate and Phosphoramidate Derivatives as Potential Anti-HIV Agents

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Dedicated to Dr. Arvind A. Natu (IISER-Pune) on the occasion of his 65th birthday

HIV protease is a promising drug target for AIDS therapy, and several potent HIV-1 protease inhibitors have been reported to date. Although existing inhibitors exhibit high selectivity, they have also been associated with severe side effects and the possible emergence of therapeutic resistance. As HIV protease cleaves the peptide bond via a tetrahedral intermediate, various transition-state models such as hydroxyethylamine (HEA) have been designed. We therefore pursued an efficient synthesis of an HEA isostere; this was performed with a novel one-pot reduction–transimination–reduction reaction sequence as a key step. α-Aminophosphonate and phosphoramidate derivatives of the HEA isostere were designed and synthesized, and all of the synthesized derivatives were assayed for their anti-HIV activities against wild-type and mutant HIV strains. Phosphoramidate derivative **15a** was found to be the most active of all synthesized compounds against the III_B and RES056 strains. As phosphonates are known to exhibit physiological stability, good cell permeability, and other promising pharmacokinetic characteristics, our newly synthesized compounds have the potential as alternatives to existing therapeutics and diagnostics.

Introduction

Acquired immune deficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). AIDS has become a pandemic which is escalating at an alarming rate.[1] UNAIDS and WHO estimate that 25 million people have died due to AIDS since its first report. It was estimated that about 34 million people were found to be living with HIV/AIDS, 2.7 million people were newly infected, and approximately 1.8 million died due to this disease in 2010 alone.[2]

HIV protease has been found to be one of several potential drug targets for AIDS therapy.[3a] Inhibition of HIV protease leads to the formation of immature noninfectious virions.[3b] Several potent HIV-1 protease inhibitors have been reported,[4,5] and there are presently many clinically approved protease inhibitors (Figure 1). Although the existing inhibitors are highly selective, they are also reported to possess side effects such as lipodystrophy, hyperlipidemia, insulin resistance,[1h,6] and emergence of resistant mutants upon prolonged use.[7]

HIV proteases are very important for the life cycle of HIV, which possesses a C_2-symmetric homodimeric structure that selectively cleaves the Phe-Pro (Tyr-Pro) moiety of the virus protein.[8] Inhibition of HIV protease is a well-known strategy for the development of new anti-HIV agents.[3,4] HIV protease cleaves the peptide bond via a tetrahedral intermediate, during which water plays an important role.[9,10] Various inhibitors have been designed based on this transition-state, known as transition-state analogues.[5] Based on this concept of transition-state analogues, different substrate models were de-

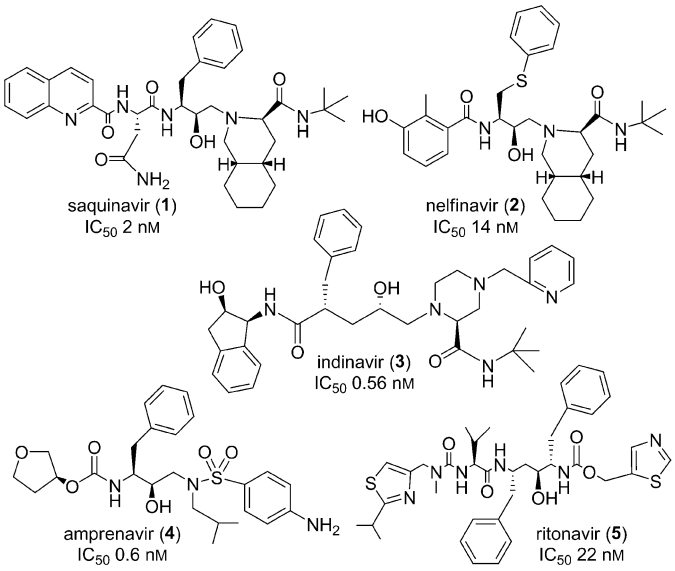

Figure 1. Clinically approved HIV protease inhibitors.

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signed. Such substrate models consist of hydroxyethylamine (HEA) **6**, statine **7**, norstatine **8**, diamino mono-ol **9**, diamino diol **10**, diamino alcohol **11**, hydroxyethylene **12**, and dihydroxyethylene isosteres **13** (Figure 2).[8]

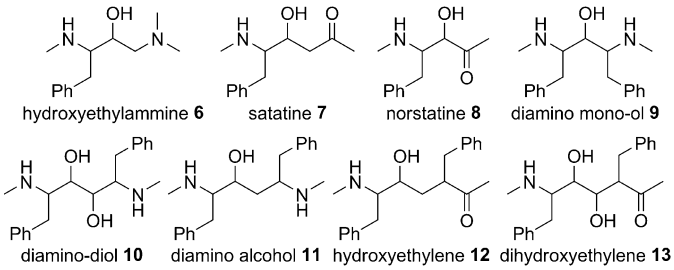


Figure 2. Substrate models for HIV protease inhibitors.

Of these substrate models, hydroxyethylamine (HEA) **6** is an attractive motif due to its low molecular weight and its use as the central core of several anti-HIV drugs, such as amprenavir **4** (Figure 1).[5,8] We opined that replacement of the P_2 pocket group of the inhibitor with aminophosphonate/phosphoramidate could result in more potent inhibitors, as phosphonates are known to be stable under physiological conditions, do not react with enzymes like cholinesterase (thus decreasing their toxicity), show good cell permeability, and increase cellular accumulation and retention of drug compounds, thus improving their therapeutic and diagnostic value.[11] Several methods have been reported for the synthesis of HEA isostere **16**;[8] however, these methods suffer from one or more drawbacks such as low overall yields, lengthy steps, and use of hazardous reagents such as lithium metal. In continuation of our interest in the design and synthesis of aminophosphonates as novel protease inhibitors,[12] we report herein an efficient synthesis of **16** and its aminophosphonate derivatives **14a–e** and phosphoramidate derivatives **15a–b** (Figure 3), with the expectation

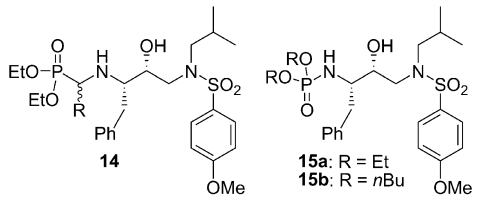
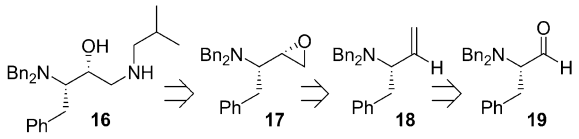


Figure 3. Designed aminophosphonate and phosphoramidate derivatives of the HEA isostere.

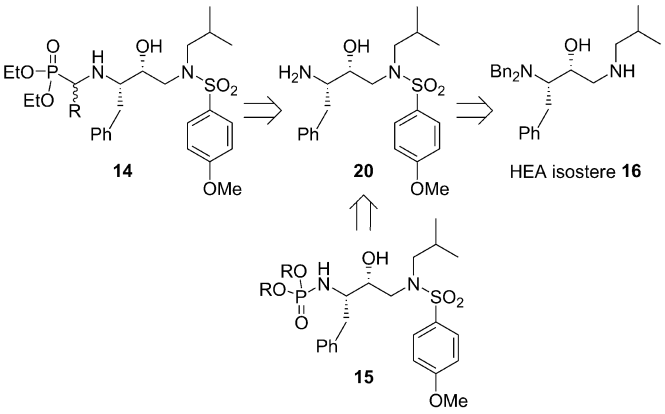
that aminophosphonate/phosphoramidate will find its place in the P_2 pocket of the enzyme and, therefore, derivatives **14** and **15** could serve as potent anti-HIV agents.

Results and Discussion

Retrosynthetically, the synthesis of HEA isostere **16** could be accomplished by the opening of epoxide **17** with isobutyl amine. The epoxide **17** could then be prepared by the epoxidation of olefin **18** which, in turn, can be obtained from corresponding aldehyde **19** using a Tebbe methylenation reaction (Scheme 1). On the other hand, α-aminophosphonate derivatives **14a–e** and phosphoramidate derivatives **15a–b** could be synthesized from the corresponding amine **20**, which could be obtained from **16** as depicted in Scheme 2.

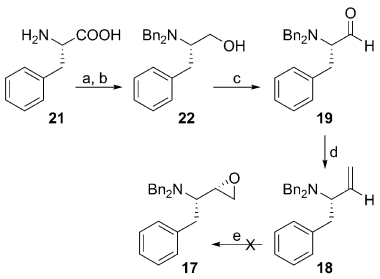


Scheme 1. Retrosynthesis of HEA isostere **16**.



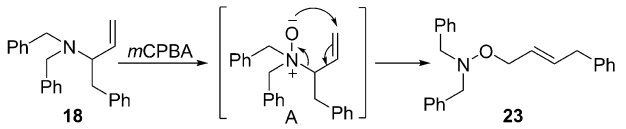
Scheme 2. Retrosynthesis of aminophosphonate **14** and phosphoramidate **15** derivatives of the HEA isostere.

We envisaged phenylalanine **21** as the starting material for the synthesis of compound **17** (Scheme 3). First, phenylalanine **21** was benzylated and subsequently reduced to dibenzyl-phenylalanol **22**, which was oxidized using Swern oxidation conditions to form aldehyde **19**.[13] Aldehyde **19** was subjected to Tebbe methylenation[14] to furnish olefin **18** in 63% yield. Reaction of olefin **18** with *m*-CPBA did not give the corresponding epoxide **17**, but it furnished a rearranged product which was



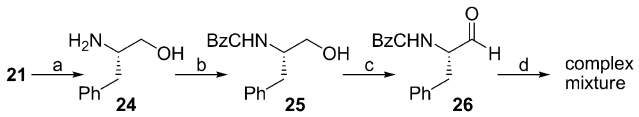
Scheme 3. *Reagents and conditions*: a) NaOH, K_2CO_3, H_2O, BnBr, reflux, 3 h; b) LAH, Et_2O, 0 °C, overnight, 60% after two steps; c) $(COCl)_2$, DMSO, CH_2Cl_2, −78→0 °C, Et_3N, 1 h, 98%; d) Tebbe reagent, THF, 0 °C, 30 min, 63%; e) *m*-CPBA, 0 °C, CH_2Cl_2.

identified as **23** (60%) by its spectral data. The formation of rearranged product **23** could be due to the fact that olefin **18** is a tertiary amine which undergoes N-oxidation reaction followed by a Meisenheimer rearrangement[15] (Scheme 4).



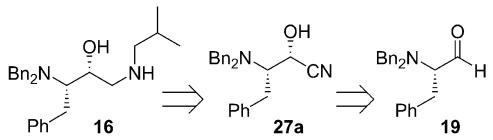
Scheme 4. Meisenheimer rearrangement.

To access the desired epoxide **17**, we decided to change the protecting group strategy for the amine group. Therefore, we thought that a carboxybenzyl (Cbz) group could be effective as a protecting group instead of a dibenzyl group. We began our synthesis by LAH reduction of phenylalanine **21** to amino alcohol **24**, followed by Cbz protection[16] to furnish compound **25**. Compound **25** was then subjected to Swern oxidation to yield amino aldehyde **26**. Unfortunately, reaction of aldehyde **26** with Tebbe reagent[14] resulted in the formation of a complex mixture. This could be attributed to the instability of amino aldehydes and the reactive nature of the Tebbe reagent (Scheme 5).

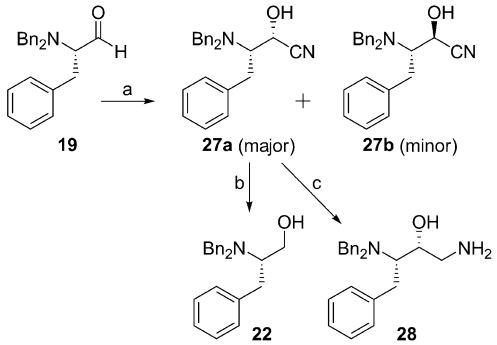


Scheme 5. *Reagents and conditions*: a) LAH, THF, 0 °C→reflux, 73%; b) CBZ-Cl, $Bi(NO_3)_3 \cdot 5H_2O$, MeOH, 30 min, 90%; c) $(COCl)_2$, DMSO, −78→0 °C, Et_3N, 1 h, 82%; d) Tebbe reagent.

Hence, we once again changed our synthetic strategy and postulated that our target compound (HEA isostere **16**) could be synthesized from cyanohydrin **27a** which, in turn, can be accessed from aldehyde **19** (Scheme 6). Aldehyde **19** was subjected to Lewis acid-catalyzed cyanohydrin formation using TMSCN and $BF_3 \cdot Et_2O$ to furnish **27a** as the major diastereomer (Scheme 7).[17] The stereochemistries of compounds **27a** and **27b** were confirmed by their spectral data. In compound **27a**, the proton of C*H*OH appearing at $\delta = 3.98$ ppm (d) showed a coupling constant of 5.4 Hz while that of **27b** ($\delta = 4.25$ ppm, d) exhibited a higher coupling constant (8.1 Hz), thereby indicating that the stereochemistries in compound **27a** and **27b** are (*S*,*S*) and (*R*,*R*), respectively, which is in accordance with published data.[18] The cyanohydrin **27a**, having the desired stereochemistry, was subjected to LAH reduction at 0 °C; however, decyanated alcohol **22** was obtained as a major product (60%). Finally, synthesis of compound **28** was achieved by the reduction of cyanohydrin **27a** by in situ-generated nickel boride,[19] albeit in moderate yield. In order to achieve the synthesis of desired isostere **16**, two other subsequent reactions on compound **28**, namely imine formation with isobutyraldehyde followed by reduction of imine with $NaBH_4$, would be required. As compound **28** was obtained in 50% yield, and two further reactions needed to be performed for the ultimate synthesis of isostere **16**, this route was found to be not lucrative enough and, therefore, we decided to develop a one-pot method.



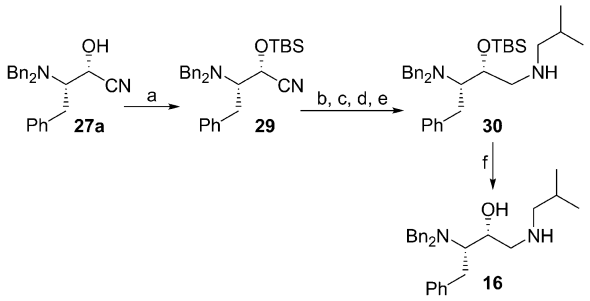
Scheme 6. Alternative retrosynthesis of HEA isostere **16**.



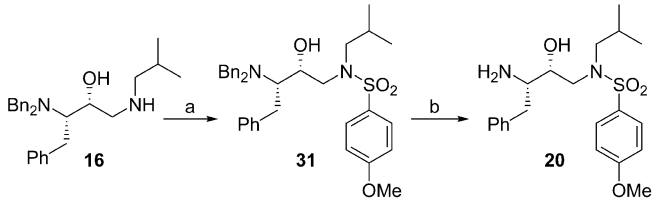
Scheme 7. *Reagents and conditions*: a) TMSCN, $BF_3 \cdot Et_2O$, CH_2Cl_2, −20 °C, 2 h, 80%; b) LAH, THF, 0 °C, 1 h, 60%; c) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 0 °C, 1 h, 50%.

One-pot reduction–transimination–reduction

In a one-pot reduction–transimination–reduction approach, the cyano group is initially reduced by DIBAL-H at −78 °C, followed by reaction with methanolic ammonium bromide which converts iminium aluminum complex into the free N–H imine. This primary imine is then converted into a more stable secondary imine by a transimination reaction.[20] Afterward, reduction of the secondary imine with $NaBH_4$ is carried out in the same pot to furnish the secondary amine. We decided to carry out synthesis of isostere **16** following this approach. We began our synthesis with the TBS protection of cyanohydrin **27a** by treating it with TBSCl to furnish compound **29**. The reduction–transimination–reduction reaction was employed on protected cyanohydrin **29** (Scheme 8) obtaining amine **30** in good yield (75%). The TBS group was deprotected with TBAF in THF solution (1 M) to furnish desired isostere **16**. Thus, we were successful in developing a one-pot reduction–transimination–reduction approach for the synthesis of isostere **16**. This isostere was then subjected to N-sulfonylation[4m] with aqueous sodium carbonate in dichloromethane to afford compound **31** which, upon benzyl deprotection with $Pd(OH)_2$/C and H_2, furnished free amine **20** (Scheme 9).



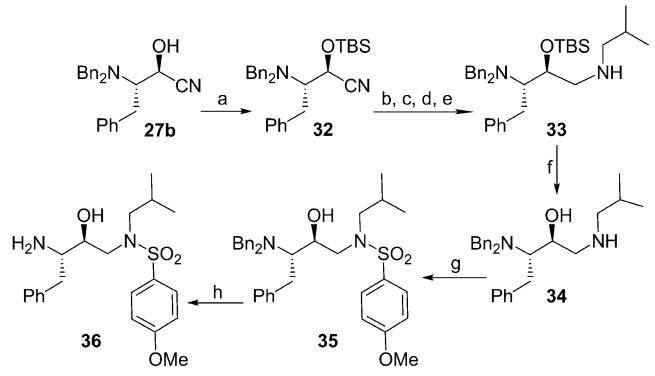
Scheme 8. *Reagents and conditions*: a) TBSCl, Imidazole, CH_2Cl_2, RT, overnight, 93%. b) DIBAL-H, Et_2O, −78 °C, 3 h; c) NH_4Br in MeOH; d) isobutyl amine, 3 h; e) $NaBH_4$, 75% in four steps; f) TBAF, THF, 85%.



Scheme 9. *Reagents and conditions*: a) 4-Methoxysulfonylchloride, CH_2Cl_2, $Na_2CO_{3(aq)}$, 3 h, 71%; b) $Pd(OH)_2/C$, H_2, 1 atm, overnight, 85%.

Confirmation of the stereochemistry of HEA isosteres 16 and 36

The spectral data for HEA isostere **16** were compared with published values,[21] and were found to be in good agreement with the reported data. This clearly proved that the stereocenter of the hydroxy group was α-oriented. Moreover, when the similar sets of reactions were performed on minor diastereomer **27b**, as depicted in Scheme 10, compound **36** was obtained as a crystalline solid. X-ray crystal structure analysis[22] of compound **36** unambiguously proved the β-orientation of the hydroxy group (Figure 4). This indirectly proves that the hydroxy group of isomer **20** is α-oriented.



Scheme 10. *Reagents and conditions*: a) TBDMSCl, imidazole, CH_2Cl_2, RT, overnight, 85%; b) DIBAL-H, Et_2O, −78 °C, 3 h; c) NH_4Br in MeOH; d) isobutyl amine, 3 h; e) $NaBH_4$, overnight, 78% in four steps; f) TBAF, THF, 81%; (g) 4-methoxysulfonylchloride, CH_2Cl_2, $Na_2CO_{3(aq)}$, 3 h, 83%; h) $Pd(OH)_2/C$, H_2, 1 atm, overnight, 80%.

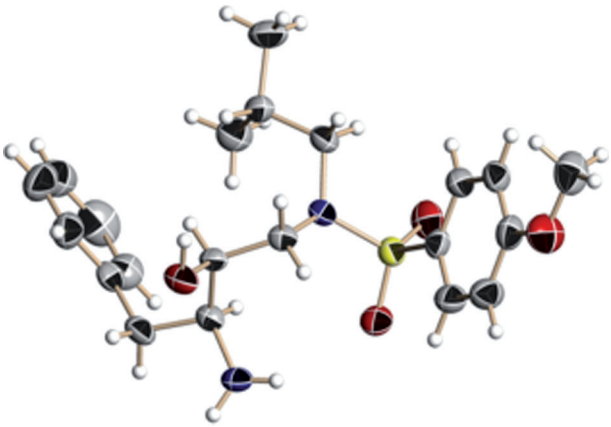
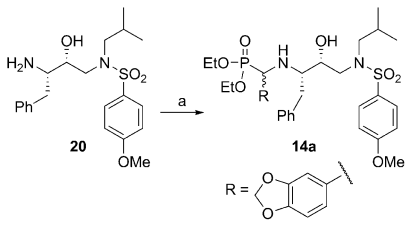


Figure 4. ORTEP diagram of compound **36**.[22]

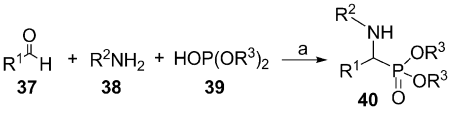
Synthesis of α-aminophosphonate and phosphoramidate derivatives of the HEA isostere

Having accomplished the synthesis of HEA isostere **16** and free amine **20**, we set out on our next aim to synthesize its α-aminophosphonate and phosphoramidate derivatives. We carried out a Kabachnik–Fields reaction of the amine with piperonal by following known methods[23] that included catalytic systems such as $TaCl_5$, $InCl_3$, and $Mg(ClO_4)_2$ under various reaction conditions. However, none of the reported methods gave the corresponding product **14a**. The reactions were limited with regard to the formation of imine, and unreacted starting materials (~60%) were recovered even when the reaction was continued beyond 24 h. We then turned to one of our recently developed methods for the synthesis of α-aminophosphonates.[12c] When the reaction was repeated in the presence of Amberlite-IR120 (acidic) under neat reaction conditions, traces of product formation were observed after 24 h. We carried out the same reaction under microwave irradiation, and corresponding product **14a** was obtained in good yield within 1 min as an inseparable diastereomeric mixture (Scheme 11).



Scheme 11. *Reagents and conditions*: a) RCHO, diethyl phosphite, Amberlite-IR120 (acidic), MWI, 53%.

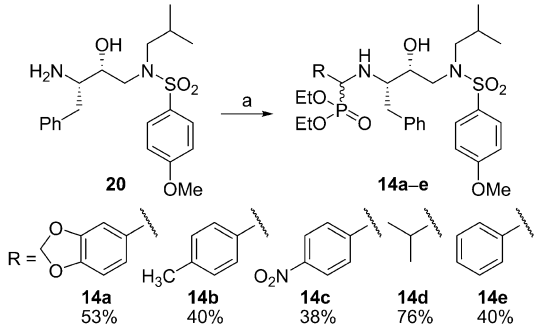
Most of the catalytic systems reported for the Kabachnik–Fields reaction use aromatic aldehydes and aromatic amines; there are very few reports for the reaction of aromatic aldehydes and aliphatic amines.[24] Hence, we proposed that Amberlite-IR120 under microwave irradiation[12c] would be a good alternative for the synthesis of α-aminophosphonate deriva-



Scheme 12. *Reagents and conditions*: a) Amberlite-IR 120 (acidic), MWI.

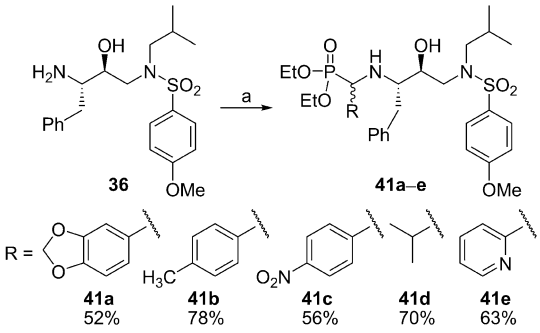
tives of isostere **16** using Kabachnik–Fields reaction (Scheme 12).

Free amine **20** was treated with diverse aldehydes and diethylphosphite under microwave irradiation in the presence of Amberlite-IR 120 as a solid catalyst to furnish corresponding α-aminophosphonates **14a–e** as mixtures of diastereomers (Scheme 13). However, these diastereomers were found to be inseparable by column chromatography as well as by preparative thin layer chromatography. Thus, the diastereomeric ratio was calculated from ^{1}H NMR spectral data.

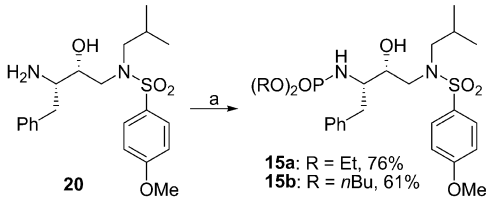


Scheme 13. *Reagents and conditions*: a) RCHO, diethyl phosphite, MWI, Amberlite-IR 120 (acidic).

Similarly, α-aminophosphonate derivatives of HEA isostere **41a–e** having a β-oriented hydroxy group were also synthesized from amine **36** by employing the above-mentioned method (Scheme 14). In addition to α-aminophosphonate derivatives, we decided to synthesize phosphoramidate derivatives **15a–b**. Amine **20** was subjected to Atherton–Todd[25] reaction conditions (Scheme 15) with diethylphosphite or dibutylphosphite to furnish the desired phosphoramidate derivatives **15a–b**.



Scheme 14. *Reagents and conditions*: a) RCHO, diethyl phosphite, MWI, Amberlite-IR 120 (acidic).



Scheme 15. *Reagents and conditions*: a) DEP or DBP, CCl_4, K_2CO_3, CH_2Cl_2.

Biological activity

All synthesized α-aminophosphonate and phosphoramidate derivatives of HEA (**14a–e** and **41a–e**) and (**15a–b**), respectively, were assayed for biological activity against wild-type HIV-1 strain III_B and HIV-2 strain ROD, along with the double mutant strains RES056 (K103N + Y181C), according to the MTT method in MT-4 cells.[26] The results of the bioassay of all the compounds expressed as IC_{50}, CC_{50}, and SI (selectivity index) values are summarized in Table 1. Drugs currently used in clinical treatment of HIV-1 infection, DDN/DDC and DMP266, were used as controls.

Table 1. Bioassay of our synthesized compounds against HIV-1 in MT-4 cells.

Compd	Strain[a]	IC_{50} [μg mL^{-1}][b]	CC_{50} [μg mL^{-1}][c]	SI[d]
14a	III_B	>13.20	13.20	<1
	ROD	>13.20	13.20	<1
14b	III_B	>2.47	2.47	<1
	ROD	>2.47	2.47	<1
14c	III_B	>14.24	14.24	<1
	ROD	>14.24	14.24	<1
14d	III_B	>11.52	11.52	<1
	ROD	>11.52	11.52	<1
14e	III_B	>13.25	13.25	<1
	ROD	>13.25	13.25	<1
41a	III_B	>13.73	13.73	<1
	ROD	>13.73	13.73	<1
41b	III_B	>4.94	4.94	<1
	ROD	>4.94	4.94	<1
41c	III_B	>3.94	3.94	<1
	ROD	>3.94	3.94	<1
41d	III_B	>13.68	13.68	<1
	ROD	>13.68	13.68	<1
41e	III_B	>13.93	13.93	<1
	ROD	>13.93	13.93	<1
15a	III_B	7.77	64.50	8
	RES056	7.40	64.50	9
	ROD	>64.50	64.50	<1
15b	III_B	>13.08	13.08	<1
	RES056	>13.08	13.08	<1
DDN/DDC	III_B	0.37	0.04	>55
	ROD	0.49	0.16	>41
DMP266	III_B	0.0018	0.0001	>1133
	RES056	0.17	0.01	>12

[a] III_B: wild-type HIV-1; ROD: HIV-2; RES056: double mutant (K103N + Y181C). [b] IC_{50}: compound concentration required to effect 50% protection of MT-4 cells against HIV-induced cytotoxicity as determined by MTT assay. [c] CC_{50}: concentration required to decrease the viability of mock-infected cells by 50% as determined by MTT assay. [d] Selectivity index (CC_{50}/IC_{50}).

The results summarized in Table 1 indicate that phosphoramidate derivative **15a** was the most active amongst all the synthesized compounds against the III_B and RES056 strains. Interestingly, compound **15a** was inactive against HIV-2; it was found to be active against HIV-1 and double mutant strain RES056 with IC_{50} values of 7.77 and 7.40 μg mL^{-1} and selectivity factors of 8 and 9, respectively. The synthesized α-aminophosphonate derivatives of HEA (**14a–e** and **41a–e**) did not show any significant activity against HIV-1 (IIIB) or HIV-2 (ROD), with IC_{50} values greater than the corresponding CC_{50} values, rendering SI values less than 1.

Conclusions

In summary, we have accomplished an efficient synthesis of the HEA isostere, a substrate model for the transition-state analogue of anti-HIV agents, by developing a novel one-pot reduction–transimination–reduction reaction sequence as a key step. Further, α-aminophosphonate and phosphoramidate derivatives of HEA isostere were designed and synthesized. The efficacy of all synthesized α-aminophosphonate and phosphoramidate derivatives were assayed for their anti-HIV activities against several strains. Phosphoramidate derivative **15a** was found to be the most active of all the synthesized compounds against III_B and RES056 strains.

Experimental Section

Chemistry

General: FT-IR spectra were recorded on an FT-IR-8300 Shimadzu spectrometer, and microanalyses were carried out on a Carlo–Erba instrument. NMR spectra were recorded on Bruker ACF200 and AV200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR) and AV400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometers, using $CDCl_3$ as solvent. Tetramethylsilane ($\delta = 0.00$ ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ ($\delta = 77.0$ ppm) in ^{13}C NMR, respectively. Chemical shifts are expressed in parts per million (ppm). In the case of NMR data for mixtures of diastereomers, the peaks corresponding to one isomer are given. Mass spectra were recorded on an LC–MS/MS-TOF API QSTAR PULSAR spectrometer, samples were introduced by an infusion method using the electrospray ionization (ESI) technique. Optical rotations were recorded on a JASCO P-1020 polarimeter. All other chemicals were of analytical grade.

(*S*)-*N*,*N*-Dibenzyl-1-phenylbut-3-en-2-amine (18): A round-bottom flask equipped with a magnetic stirring bar and oil bubbler was charged with titanocene dichloride (250 mg, 1.0 mmol) and flushed with argon, then $AlMe_3$ (2.0 M in PhMe, 1 mL) was added dropwise. The resulting dark red mixture was stirred at room temperature with initial evolution of CH_4 through the bubbler. Stirring was continued for 3 days. The flask was cooled to 0 °C, to which was added a solution of **19** (329 mg, 1 mmol) in THF (4 mL). The reaction was allowed to warm to room temperature, and stirring was continued for 30 min. After completion of the reaction (as assessed by TLC), the reaction mixture was diluted with diethyl ether (10 mL) followed by the slow addition of aq. NaOH (1 mL) until gas evolution ceased. Then, Na_2SO_4 was added to the reaction mixture, it was filtered, and the filtrate was concentrated to give the crude product, which was purified by column chromatography over silica gel using EtOAc/petroleum ether (PE) (2:98) as eluent to furnish olefin **18** as a colorless syrup (205 mg, 63%): $R_f = 0.65$ (EtOAc/PE, 1:9); $[\alpha]^{20}_D = +17.6$ ($c = 1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3063$, 3024, 2933, 2833, 2802, 1602, 1494, 1454, 1217, 1120 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.75$–3.01 (ABX, $J = 13.6$ Hz, $J = 7.4$ Hz, $J = 6.2$ Hz, 2H), 3.42–3.80 (AB, $J = 13.9$ Hz, 4H), 3.32–3.43 (m, 1H), 5.00 (ddd, $J = 2.0$ Hz, $J = 1.0$ Hz, $J = 17.2$ Hz, 1H), 5.22 (ddd, $J = 10.4$ Hz, $J = 0.6$ Hz, $J = 2.0$ Hz, 1H), 5.85 (ddd, $J = 17.2$ Hz, $J = 10.4$ Hz, $J = 2.3$ Hz, 1H), 7.00–7.23 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 38.4$, 53.6, 62.2, 118.1, 125.9, 126.8, 128.1, 128.2, 128.6, 129.6, 135.9, 139.7, 140.2 ppm; MS (ESI): *m/z* 328.2 $[M+H]^+$; Anal. calcd for $C_{24}H_{25}N$: C 88.03, H 7.70, N 4.28, found: C 88.15, H 7.77, N 4.23.

(*E*)-*N*,*N*-Dibenzyl-*O*-(4-phenylbut-2-enyl)hydroxylamine (23): *m*-CPBA (46 mg, 0.27 mmol) was added to a solution of alkene **18** (80 mg, 0.244 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 1 h. After completion of the reaction (as assessed by TLC), water (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude product, which was purified by flash chromatography using EtOAc/PE (3:97) to furnish pure product **23** as a colorless syrup (50 mg, 60%): $R_f = 0.50$ (EtOAc/PE, 1:9); IR ($CHCl_3$): $\tilde{\nu} = 3065$, 3019, 2926, 2910, 1602, 1494, 1454, 1217, 1030 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.15$ (d, $J = 6.7$ Hz, 2H), 3.65 (dd, $J = 6.4$, 6.6 Hz, 2H), 3.77 (s, 4H), 5.11–5.25 (m, 1H), 5.40–5.54 (m, 1H), 7.00–7.31 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 38.8$, 62.9, 74.3, 126.1, 127.1, 127.3, 128.2, 128.4, 128.6, 129.8, 133.5, 137.9, 140.1 ppm; MS (ESI): *m/z* 344.2 $[M+H]^+$, 366.2 $[M+Na]^+$; Anal. calcd for $C_{24}H_{25}NO$: C 83.93, H 7.34, N 4.08, found: C 83.83, H 7.31, N 4.15.

Hydrocyanation of aldehyde 19: A mixture of aldehyde **19** (1.97 g, 6 mmol), trimethylsilylcyanide (750 μL, 7.2 mmol) and $BF_3{\cdot}Et_2O$ (1 mL, 7.2 mmol) in dry CH_2Cl_2 (50 mL) was stirred at −20 °C for 2 h. After completion of the reaction (as assessed by TLC), the reaction mixture was poured into water (50 mL), and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield crude product, which was chromatographed on silica gel using EtOAc/PE (5:95) as eluent to furnish pure **27a** (2.1 g, 80%) and **27b** (0.21 g, 10%) as the major and minor products, respectively.

(2*S*,3*S*)-3-(Dibenzylamino)-2-hydroxy-4-phenylbutanenitrile (27a): Colorless syrup (2.1 g, 80%): $R_f = 0.32$ (EtOAc/PE, 1:9); $[\alpha]^{20}_D = +48.4$ ($c = 1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3421$, 3064, 3020, 2928, 2841, 2401, 1602, 1521, 1494, 1454, 1375, 1215, 1074, 1028 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.94$–3.01 (m, 1H), 3.18–3.34 (m, 2H), 3.52 (d, $J = 13.1$ Hz, 2H), 3.98 (d, $J = 5.4$ Hz, 1H), 4.21 (d, $J = 13.1$ Hz, 2H), 7.20–7.41 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 31.4$, 54.6, 59.6, 61.1, 119.5, 127.1, 127.9, 128.9, 129.0, 129.1, 129.3, 136.8, 137.8 ppm; MS (ESI): *m/z* 357.3 $[M+H]^+$, 379.3 $[M+Na]^+$; Anal. calcd for $C_{24}H_{24}N_2O$: C 80.87, H 6.79, N 7.86, found: C 80.95, H 6.83, N 7.73.

(2*R*,3*S*)-3-(Dibenzylamino)-2-hydroxy-4-phenylbutanenitrile (27b): Colorless syrup (0.21 g, 10%): $R_f = 0.25$ (EtOAc/PE, 1:9); $[\alpha]^{20}_D = +47.0$ ($c = 1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3400$, 3020, 2400, 1602, 1521, 1495, 1454, 1375, 1215, 1074, 1028 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.95$–3.09 (m, 2H), 3.25–3.33 (m, 1H), 3.42–3.89 (AB, $J = 13.3$ Hz, 4H), 4.25 (d, $J = 8.1$ Hz, 1H), 7.15–7.40 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 32.4$, 54.2, 61.8, 62.5, 119.2, 127.1, 127.7, 128.8, 128.9, 129.0, 129.4, 138.0, 138.1 ppm; MS (ESI): *m/z* 357.3 $[M+H]^+$, 379.3 $[M+Na]^+$; Anal. calcd for $C_{24}H_{24}N_2O$: C 80.87, H 6.79, N 7.86, found: C 80.93, H 6.59, N 7.75.

(2*S*,3*S*)-1-Amino-3-(dibenzylamino)-4-phenylbutan-2-ol (28): $NaBH_4$ (160 mg, 4.2 mmol) was added slowly to a suspension of cyanohydrin **27a** (150 mg, 0.42 mmol) and $NiCl_2{\cdot}6H_2O$ (200 mg, 0.84 mmol) in MeOH (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion of reaction (as assessed by TLC), aq. HCl (3 N) was added until the black precipitate dissolved. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in water and was made alkaline using aq. NaOH (1 N) and the product was extracted with EtOAc (3×10 mL), dried over Na_2SO_4, and concentrated in vacuo to give the crude product, which was chromatographed over silica gel using EtOAc as eluent to furnish product **28** as a colorless syrup (75 mg, 50%): $R_f = 0.54$ (EtOAc/PE, 3:7); $[\alpha]^{20}_D = +6.55$ ($c = 1.1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3350, 3019, 1602, 1495, 1453, 1216\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.43–2.55$ (m, 1H), 2.67–2.84 (m, 2H), 2.95–3.15 (m, 1H), 3.35–3.88 (m, 4H), 3.46 (bs, 2H), 3.96–4.18 (m, 2H), 7.15–7.34 ppm (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 32.7, 44.9, 54.6, 61.7, 71.8, 125.8, 127.0, 128.3, 128.9, 129.6, 139.9, 141.6$ ppm; MS (ESI): *m/z* 361.2 $[M+H]^+$; Anal. calcd for $C_{24}H_{28}N_2O$: C 79.96, H 7.83, N 7.77, found: C 80.06, H 7.95, N 7.68.

(2*S*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanenitrile (29): TBSCl (13 g, 85 mmol) was added to a solution of cyanohydrin **27a** (20 g, 57 mmol) and imidazole (10 g, 143 mmol) in CH_2Cl_2 (100 mL) at 0 °C, and the reaction mixture was stirred overnight at room temperature. After completion of the reaction (as assessed by TLC), water (100 mL) was added, and the product was extracted with CH_2Cl_2 (3×100 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give the crude product, which was chromatographed over silica gel using EtOAc/PE (5:95) as eluent to furnish product **29** as a colorless syrup (25 g, 93%): $R_f = 0.53$ (EtOAc/PE, 1:4); $[\alpha]^{20}_D = -34.23$ ($c = 0.95$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3063, 2955, 2858, 2357, 1602, 1494, 1469, 1369, 1263, 1122\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.00$ (s, 3H), 0.06 (s, 3H), 0.78 (s, 9H), 2.87–2.91 (m, 2H), 3.22–3.32 (m, 1H), 3.51–3.67 (m, 4H) 4.36 (d, $J = 5.8$ Hz, 1H), 7.03–7.16 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.2, -5.0, 18.1, 25.7, 33.2, 55.0, 63.3, 63.6, 120.0, 126.5, 127.2, 128.3, 128.5, 128.8, 129.6, 139.0, 139.2$ ppm; MS (ESI): *m/z* 471.9 $[M+H]^+$, 493.9 $[M+Na]^+$; Anal. calcd for $C_{30}H_{38}N_2OSi$: C 76.55, H 8.14, N 5.95, found: C 76.65, H 8.20, N 5.86.

(2*S*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanenitrile (30): A 1 M solution of DIBAL-H in hexane (2.5 mL, 2.5 mmol) was added to a cooled solution (−78 °C) of cyanohydrin **29** (470 mg, 1 mmol) in dry ether (8 mL). After stirring at −78 °C for 3 h, NH_4Br (240 mg) in dry MeOH (4 mL) was added. The cooling bath was removed, isobutyl amine (500 μL, 5 mmol) was added, and stirring was continued for another 3 h at room temperature. The reaction mixture was cooled in an ice bath, and $NaBH_4$ (74 mg, 2 mmol) was added in three portions, then the mixture was stirred overnight at room temperature. Water (20 mL) was added, and the product was extracted with diethyl ether (3×25 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated to furnish the crude product, which was chromatographed using EtOAc/PE (5:95) to afford product **30** as a colorless syrup (398 mg, 75%): $R_f = 0.40$ (EtOAc/PE, 1:9); $[\alpha]^{20}_D = -10.95$ ($c = 1.0$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3063, 3018, 2955, 2856, 1602, 1494, 1454, 1361, 1255, 1215, 1120\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.00$ (s, 3H), 0.01 (s, 3H), 0.67 (d, $J = 6.6$ Hz, 3H), 0.69 (d, $J = 6.7$ Hz, 3H), 0.80 (s, 9H), 1.32–1.52 (m, 1H), 2.03–2.21 (m, 2H), 2.43–2.48 (m, 2H), 2.68–2.89 (m, 2H), 3.01–3.09 (m, 1H), 3.47–3.65 (AB, $J = 8.2$ Hz, 4H), 3.95–4.02 (m, 1H), 7.01–7.12 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -4.2, -3.2, 18.3, 20.7, 20.8, 26.1, 28.4, 32.6, 54.6, 54.7, 58.3, 62.0, 72.2, 125.6, 126.7, 128.1, 128.8, 129.8, 140.3, 142.0$ ppm; MS (ESI): *m/z* 531.8 $[M+H]^+$, 553.8 $[M+Na]^+$; Anal. calcd for $C_{34}H_{50}N_2OSi$: C 76.93, H 9.49, N 5.28, found: C 76.79; H 9.60; N 5.33.

(2*R*,3*S*)-3-(Dibenzylamino)-1-(isobutylamino)-4-phenylbutan-2-ol (16): TBAF in THF (1 mL, 1.0 mmol) was added to the solution of **30** (150 mg, 0.28 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature. After completion of the reaction (as assessed by TLC), THF was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc/PE (2:3) as eluent to obtain **16** as a colorless syrup (100 mg, 85%): $R_f = 0.20$ (EtOAc/PE, 1:9); $[\alpha]^{20}_D = +4.71$ ($c = 1.05$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3371, 3019, 2960, 2872, 2806, 1602, 1494, 1454, 1215\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J = 6.7$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H), 1.62–1.69 (m, 1H), 2.28–2.36 (m, 1H), 2.37–2.42 (m, 1H), 2.46–2.52 (m, 1H), 2.74–2.90 (m, 2H), 2.98–3.04 (m, 2H), 3.24 (bs, 2H), 3.57–3.73 (AB, $J = 13.9$ Hz, 4H), 3.86–3.91 (m, 1H), 7.08–7.32 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.5, 28.1, 32.7, 53.0, 54.6, 57.2, 62.3, 68.6, 125.8, 126.9, 128.2, 128.3, 128.9, 129.7, 139.9, 141.5$ ppm; MS (ESI): *m/z* 417.5 $[M+H]^+$, 439.5 $[M+Na]^+$; Anal. calcd for $C_{28}H_{36}N_2O$: C 80.73, H 8.71, N 6.72, found: C 80.79, H 8.75, N 6.77.

***N*-((2*R*,3*S*)-3-(Dibenzylamino)-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (31)**: A solution of Na_2CO_3 (81 mg, 0.77 mmol) in water (500 μL) was added to a solution of **16** (200 mg, 0.48 mmol) in CH_2Cl_2 (2 mL) at 0 °C. A solution of *p*-methoxysulfonyl chloride (99 mg, 0.48 mmol) in CH_2Cl_2 (1 mL) was added to this stirred solution at 0 °C. The reaction was allowed to warm to room temperature. After completion of the reaction (as assessed by TLC), water (5 mL) was added, and the product was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to obtain the crude product, which was chromatographed over silica gel using EtOAc/PE (1:9) as eluent to give **31** as a colorless syrup (200 mg, 71%): $R_f = 0.60$ (EtOAc/PE, 1:3); $[\alpha]^{20}_D = -1.44$ ($c = 1.0$ in MeOH); IR ($CHCl_3$): $\tilde{\nu} = 3479, 3019, 2966, 1597, 1496, 1215, 1153, 1028\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.84$ (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.63 (bs, 1H), 1.77–1.82 (m, 1H), 2.65–2.95 (m, 4H), 2.99–3.08 (m, 3H), 3.60–3.76 (AB, $J = 13.9$ Hz, 4H), 3.87 (s, 3H), 4.07–4.17 (m, 1H), 6.92 (d, $J = 8.9$ Hz, 2H), 7.12–7.31 (m, 15H), 7.58 ppm (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.9, 20.2, 27.3, 32.1, 54.6, 55.5, 55.6, 58.8, 62.4, 70.6, 114.2, 125.9, 126.9, 128.2, 128.3, 128.7, 129.5, 129.8, 130.6, 139.9, 141.0, 162.9$ ppm; MS (ESI): *m/z* 587.5 $[M+H]^+$, 589.5 $[M+Na]^+$, 609.5 $[M+K]^+$; Anal. calcd for $C_{35}H_{42}N_2O_4S$: C 71.64, H 7.21, N 4.77, found: C 71.74, H 7.35, N 4.83.

***N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (20)**: A mixture of **31** (500 mg, 0.85 mmol) and a catalytic amount of $Pd(OH)_2$ in MeOH (5 mL) were subjected to hydrogenation at 1 atm for 24 h at room temperature. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of PE/EtOAc (3:7) to furnish **20** as a colorless syrup (293 mg, 85%): $R_f = 0.10$ (EtOAc/PE, 1:3); $[\alpha]^{20}_D = +16.28$ ($c = 0.90$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3479, 3018, 2968, 1597, 1496, 1334, 1261, 1215, 1153\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.88$ (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 1.82–1.96 (m, 1H), 2.48–2.54 (m, 1H), 2.81–3.03 (m, 3H), 3.07–3.35 (m, 3H), 3.73–3.76 (m, 1H), 3.86 (s, 3H), 6.98 (d, $J = 8.9$ Hz, 2H), 7.19–7.32 (m, 5H), 7.75 ppm (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.9, 20.2, 39.1, 52.6, 55.6, 55.7, 58.5, 73.1, 114.3, 126.4, 128.6, 129.3, 129.5, 130.3, 138.9, 162.9$ ppm; MS (ESI):

m/z 407.4 $[M+H]^+$, 429.4 $[M+Na]^+$; Anal. calcd for $C_{21}H_{30}N_2O_4S$: C 62.04, H 7.44, N 6.89, found: C 62.09, H 7.53, N, 6.79.

(2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanenitrile (32): Title compound **32** was prepared starting from cyanohydrin **27 b**, as per the procedure outlined for the preparation of protected cyanohydrin **29**, as a colorless syrup (85%): $R_f=0.45$ (EtOAc/PE, 1:4); $[\alpha]^{20}_D=-13.9$ ($c=1.0$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3021$, 2959, 2931, 2859, 2401, 1602, 1471, 1495, 1454, 1364, 1257, 1216, 1108 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.00$ (s, 3H), 0.13 (s, 3H), 0.85 (s, 9H), 2.95–3.10 (m, 3H), 3.53–3.68 (m, 3H), 4.05–4.12 (m, 1H), 4.37–4.38 (m, 1H), 7.08–7.35 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=-5.4$, −5.1, 18.1, 25.6, 30.8, 55.3, 62,4, 64.7, 119.8, 127.1, 128.3, 128.6, 128.8, 128.9, 129.3, 138.9, 139.3 ppm; MS (ESI): *m/z* 471.9 $[M+H]^+$, 493.9 $[M+Na]^+$, 509.8 $[M+K]^+$; Anal. calcd for $C_{30}H_{38}N_2OSi$: C 76.55, H 8.14, N 5.95, found: C 76.49, H 8.28, N 6.10.

(2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanenitrile (33): Title compound **33** was prepared starting from the protected cyanohydrin **32**, as per the procedure outlined for the preparation of compound **30**, as a colorless syrup (78%): $R_f=0.35$ (EtOAc/PE, 1:9); $[\alpha]^{20}_D=+6.79$ ($c=1.2$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3020$, 2955, 1602, 1495, 1454, 1362, 1216 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta=-0.06$ (s, 3H), 0.00 (s, 3H), 0.66 (t, $J=6.8$, 7.2 Hz, 6H), 0.84 (s, 9H), 1.29–1.36 (m, 1H), 1.87–2.10 (m, 2H), 2.45–2.54 (m, 1H), 2.91–3.01 (m, 3H), 3.07–3.15 (m, 1H), 3.39 (d, $J=13.4$ Hz, 2H), 3.66–3.74 (m, 1H), 4.11 (d, $J=13.4$ Hz, 2H), 7.18–7.28 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=-4.6$, −3.9, 18.2, 20.6, 20.7, 26.1, 28.5, 30.8, 52.7, 55.9, 57.3, 59.9, 73.2, 125.9, 126.8, 128.2, 128.4, 129.2, 129.4, 140.8, 141.2 ppm; MS (ESI): *m/z* 531.8 $[M+H]^+$, 553.8 $[M+Na]^+$; Anal. calcd for $C_{34}H_{50}N_2OSi$: C 76.93, H 9.49, N 5.28, found: C 76.85, H 9.54, N 5.24.

(2*S*,3*S*)-3-(Dibenzylamino)-1-(isobutylamino)-4-phenylbutan-2-ol (34): Title compound **34** was prepared starting from the compound **33**, as per the procedure outlined for the preparation of compound **16**, as a colorless syrup (81%): $R_f=0.15$ (EtOAc/PE, 1:9); $[\alpha]^{20}_D=+8.88$ ($c=0.90$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3683$, 3338, 3019, 2958, 1602, 1521, 1495, 1454, 1216 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.82$ (d, $J=6.7$ Hz, 6H), 1.56–1.62 (m, 1H), 2.12–2.46 (m, 4H), 2.76–3.12 (m, 3H), 3.40 (d, $J=13.4$ Hz, 2H), 3.64–3.68 (m, 1H), 3.99 (d, $J=13.4$ Hz, 2H), 7.14–7.34 ppm (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=20.6$, 28.5, 31.8, 53.4, 54.4, 57.9, 61.8, 69.7, 126.2, 127.2, 128.4, 128.5, 129.1, 129.4, 139.9, 140.4 ppm; MS (ESI): *m/z* 417.5 $[M+H]^+$, 439.5 $[M+Na]^+$; Anal. calcd for $C_{28}H_{36}N_2O$: C 80.73, H 8.71, N 6.72, found: C 80.81, H 8.65, N 6.81.

***N*-((2*S*,3*S*)-3-(Dibenzylamino)-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (35)**: Title compound **35** was prepared starting from the compound **34**, as per the procedure outlined for the preparation of compound **31**, as a colorless syrup (83%): $R_f=0.45$ (EtOAc/PE, 1:3); $[\alpha]^{20}_D=+5.0$ ($c=1.0$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3515$, 3019, 2966, 1598, 1496, 1454, 1259, 1216 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.68$ (d, $J=6.2$ Hz, 6H), 1.40–1.58 (m, 1H), 2.53–2.69 (m, 3H), 2.80–2.91 (m, 1H), 2.96–3.15 (m, 2H), 3.21–3.33 (m, 1H), 3.41 (d, $J=13.4$ Hz, 2H), 3.60–3.66 (m, 1H), 3.74 (bs, 1H), 3.87 (s, 3H), 4.09 (d, $J=13.4$ Hz, 2H), 6.93 (d, $J=9.0$ Hz, 2H), 7.21–7.32 (m, 15H), 7.64 ppm (d, $J=9.0$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=19.8$, 20.0, 27.0, 30.8, 54.8, 55.0, 55.6, 57.9, 61.9, 70.0, 114.1, 126.1, 127.1, 128.3, 128.6, 129.1, 129.3, 129.4, 131.0, 139.7, 140.2, 162.7 ppm; MS (ESI): *m/z* 587.5 $[M+H]^+$, 589.5 $[M+Na]^+$, 609.5 $[M+K]^+$; Anal. calcd for $C_{35}H_{42}N_2O_4S$: C 71.64, H 7.21, N 4.77, found: C 71.76, H 7.28, N 4.86.

***N*-((2*S*,3*S*)-3-Amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (36)**: Title compound **36** was prepared starting from the compound **35**, as per the procedure outlined for the preparation of **20**, as a colorless solid (80%): $R_f=0.10$ (EtOAc/PE, 1:3); mp: 148–149 °C; $[\alpha]^{20}_D=-3.84$ ($c=1.0$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3396$, 3018, 2969, 1597, 1496, 1334, 1261, 1217, 1155 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.78$ (d, $J=6.7$ Hz, 3H), 0.80 (d, $J=6.6$ Hz, 3H), 1.61–1.75 (m, 1H), 2.37 (bs, 3H), 2.67–2.74 (m, 2H), 2.84–2.96 (m, 3H), 3.25–3.32 (m, 2H), 3.57–3.64 (m, 1H), 3.85 (s, 3H), 6.96 (d, $J=8.8$ Hz, 2H), 7.20–7.30 (m, 5H), 7.72 ppm (d, $J=8.8$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=19.9$, 20.1, 27.4, 40.6, 52.7, 53.5, 55.6, 58.7, 70.1, 114.3, 126.5, 128.6, 129.4, 130.4, 138.6, 162.9 ppm; MS (ESI): *m/z* 407.4 $[M+H]^+$, 429.4 $[M+Na]^+$; Anal. calcd for $C_{21}H_{30}N_2O_4S$: C 62.04, H 7.44, N 6.89, found: C 62.15, H 7.52, N 6.73.

General experimental procedure for the synthesis of α-aminophosphonates: The corresponding aldehyde (1 mmol), amine **20** or **36** (1 mmol), diethylphosphite (1 mmol), and Amberlite-IR 120 (100 mg) were combined in a Pyrex test tube and exposed to microwave irradiation (Kenstar OM-9918C; 2450 MHz, 2350 W). After completion of the reaction (as assessed by TLC), the reaction mixture was cooled, and CH_2Cl_2 (25 mL) was added. The catalyst was removed from the reaction mixture by filtration, and the filtrate was concentrated under vacuum. The residue was chromatographed over silica gel column (100–200 mesh) and eluted with PE/EtOAc (2:3 to 3:2) to afford the corresponding pure α-aminophosphonates.

Diethyl (*S*)-benzo[*d*][1,3]dioxol-5-yl-((2*S*,3*R*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)-methylphosphonate (14 a): Product was isolated as a 1:5 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (53%): $R_f=0.70$ (EtOAc); IR ($CHCl_3$): $\tilde{\nu}=$ 3340, 3022, 2400, 1598, 1494, 1440, 1300, 1210, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.83$ (d, $J=6.5$ Hz, 3H), 0.85 (d, $J=6.8$ Hz, 3H), 1.14 (t, $^3J_{PH}=7.0$ Hz, 3H), 1.24 (t, $^3J_{PH}=7.3$ Hz, 3H), 1.69–1.76 (m, 1H), 2.70–2.75 (m, 1H), 2.81–2.82 (m, 2H), 2.89–2.91 (m, 1H), 2.93–2.97 (m, 1H), 3.07–3.22 (m 2H), 3.51–3.55 (m, 1H), 3.71–3.98 (m, 4H), 3.89 (s, 3H), 3.96 (d, $^2J_{PH}=19.6$ Hz, 1H), 5.97 (s, 2H), 6.73–6.74 (m, 2H), 6.85 (m, 1H), 6.99 (d, $J=9.0$ Hz, 2H), 7.23–7.34 (m, 5H), 7.68 ppm (d, $J=9.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 16.3 (d, $^3J_{PC}=5.9$ Hz), 16.4 (d, $^3J_{PC}=5.9$ Hz), 19.8, 20.1, 27.2, 35.1, 52.8, 55.6, 58.3 (d, $^1J_{PC}=152.6$ Hz), 58.3, 59.2 (d, $^3J_{PC}=13.9$ Hz), 62.5 (d, $^2J_{PC}=7.3$ Hz), 62.9 (d, $^2J_{PC}=7.3$ Hz), 70.6, 101.1, 108.1, 109.0 (d, $^3J_{PC}=5.9$ Hz), 114.2, 122.6 (d, $^3J_{PC}=7.3$ Hz), 126.5, 128.5, 129.4, 129.6, 129.7, 130.4, 137.9, 147.4, 147.8, 162.8 ppm; ^{31}P NMR (161 MHz, $CDCl_3$): $\delta=23.57$ ppm; MS (ESI): *m/z* 699.5 $[M+Na]^+$; Anal. calcd for $C_{33}H_{45}N_2O_9PS$: C 58.57, H 6.70, N 4.14, found: C 58.69, H 6.81, N 4.21.

Diethyl ((2*S*,3*R*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)(*p*-tolyl) methylphosphonate (14 b): Product was isolated as a 1:4 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (40%): $R_f=0.70$ (EtOAc); IR ($CHCl_3$): $\tilde{\nu}=3351$, 3019, 1598, 1513, 1497, 1412, 1215, 1155, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.89$ (d, $J=6.5$ Hz, 3H), 0.90 (d, $J=6.4$ Hz, 3H), 1.08 (t, $^3J_{PH}=$ 7.0 Hz, 3H), 1.27 (t, $^3J_{PH}=7.3$ Hz, 3H), 1.88–1.95 (m, 1H), 2.31 (s, 3H), 2.47–2.53 (m, 1H), 2.76–2.82 (m, 2H), 2.89–3.06 (m, 2H), 3.11–3.16 (m, 1H), 3.32–3.36 (m, 1H), 3.63–3.71 (m, 1H), 3.84–4.06 (m, 4H), 3.89 (s, 3H), 3.99 (d, $^2J_{PH}=23.1$ Hz, 1H), 6.64–6.67 (m, 2H), 6.93–7.06 (m, 6H), 7.25–7.28 (m, 3H), 7.75 ppm (d, $J=8.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.2$ (d, $^3J_{PC}=5.9$ Hz), 16.4 (d, $^3J_{PC}=$ 5.9 Hz), 20.0, 20.1, 27.1, 34.8, 51.8, 55.6, 57.2 (d, $^1J_{PC}=158.5$ Hz),

57.9, 58.4 (d, $^3J_{PC}$ = 15.4 Hz), 62.4 (d, $^2J_{PC}$ = 7.3 Hz), 62.9 (d, $^2J_{PC}$ = 6.6 Hz), 69.7, 114.2, 126.6, 128.0 (d, $^3J_{PC}$ = 5.9 Hz), 128.6, 129.0, 129.4, 129.4, 131.0, 131.9, 137.4, 137.9, 162.8 ppm; ^{31}P NMR (161 MHz, $CDCl_3$): δ = 23.55 ppm; MS (ESI): *m/z* 647.9 $[M+H]^+$; Anal. calcd for $C_{33}H_{47}N_2O_7PS$: C 61.28, H 7.32, N 4.33, found: C 61.37, H 7.38, N 4.26.

Diethyl ((2*S*,3*R*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)(4-nitrophenyl)methylphosphonate (14c): Product was isolated as a 1:4 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (38%): R_f = 0.60 (EtOAc); IR ($CHCl_3$): $\tilde{\nu}$ = 3350, 3019, 2923, 1604, 1523, 1495, 1456, 1397, 1348, 1217, 1156, 1081, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 1.14 (t, $^3J_{PH}$ = 7.2 Hz, 3H), 1.22 (t, $^3J_{PH}$ = 7.2 Hz, 3H), 1.65–1.70 (m, 1H), 2.72–2.78 (m, 2H), 2.82–2.83 (m, 1H), 2.94–2.97 (m, 2H), 3.06–3.13 (m, 2H), 3.47–3.65 (m, 1H), 3.77–3.98 (m, 4H), 3.91 (s, 3H), 4.22 (d, $^2J_{PH}$ = 21.7 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H); 7.21–7.34 (m, 5H), 7.46- 7.48 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 8.18 ppm (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{PC}$ = 5.1 Hz), 16.4 (d, $^3J_{PC}$ = 5.1 Hz), 19.8, 20.1, 27.2, 36.0, 52.4, 55.6, 58.3 (d, $^1J_{PC}$ = 146.7 Hz), 58.6, 59.9 (d, $^3J_{PC}$ = 11.7 Hz), 62.9 (d, $^2J_{PC}$ = 6.6 Hz), 63.1 (d, $^2J_{PC}$ = 6.6 Hz), 71.4, 114.3, 123.4, 126.8, 128.7, 129.4, 129.4, 129.6, 129.9, 137.8, 144.5, 147.5, 163.0 ppm; ^{31}P NMR (161 MHz, $CDCl_3$): δ = 21.91 ppm; MS (ESI): *m/z* 700.6 $[M+Na]^+$; Anal. calcd for $C_{32}H_{44}N_3O_9PS$: C 56.71, H 6.54. N 6.20, found: C 56.83, H 6.62, N 6.36.

Diethyl 1-((2*S*,3*R*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)-2-methylpropylphosphonate (14d): Product was isolated as a 1:4 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (76%): R_f = 0.20 (EtOAc/PE, 1:1); IR ($CHCl_3$): $\tilde{\nu}$ = 3349, 3019, 2966, 2873, 1598, 1579, 1497, 1465, 1391, 1337, 1260, 1216, 1154, 1093, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.59 (d, *J* = 6.8 Hz, 3H), 0.60 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 1.28–1.33 (m, 6H), 1.77–1.83 (m, 1H), 2.03–2.10 (m, 1H), 2.53–2.61 (m, 2H), 2.82–3.04 (m, 4H), 3.17–3.23 (m, 1H), 3.47–3.63 (m, 1H), 3.82–3.84 (m, 1H), 3.86 (s, 3H), 3.93–4.18 (m, 4H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.23–7.34 (m, 5H), 7.78 ppm (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (d, $^3J_{PC}$ = 5.9 Hz), 16.6 (d, $^3J_{PC}$ = 5.9 Hz), 17.3 (d, $^3J_{PC}$ = 2.9 Hz), 20.0, 20.1, 26.9, 29.5 (d, $^2J_{PC}$ = 3.7 Hz), 34.4, 51.1, 55.5, 57.2, 57.7 (d, $^1J_{PC}$ = 162.1 Hz), 61.6 (d, $^2J_{PC}$ = 8.1 Hz), 62.6 (d, $^2J_{PC}$ = 10.3 Hz), 63.2 (d, $^2J_{PC}$ = 7.3 Hz), 69.4, 114.2, 126.7, 128.7, 129.3, 129.4, 131.6, 138.6, 162.7 ppm; ^{31}P NMR (161 MHz, $CDCl_3$): δ = 27.36 ppm; MS (ESI): *m/z* 621.5 $[M+Na]^+$; Anal. calcd for $C_{29}H_{47}N_{32}O_7PS$: C 58.17, H 7.91, N 4.68, found: C 58.28, H 7.98, N 4.77.

Diethyl ((2*S*,3*R*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)(phenyl)methylphosphonate (14e): Product isolated as a 1:3 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (40%): R_f = 0.70 (EtOAc); IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 3019, 1598, 1497, 1335, 1260, 1215, 1154 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 1.07 (t, $^3J_{PH}$ = 7.1 Hz, 3H), 1.21 (t, $^3J_{PH}$ = 7.1 Hz, 3H), 1.61–1.76 (m, 1H), 2.66–2.76 (m, 1H), 2.78–2.86 (m, 2H), 2.90–2.91 (m, 1H), 2.94–2.97 (m, 1H), 3.05–3.23 (m, 2H), 3.48–3.54 (m, 1H), 3.63–4.05 (m, 4H), 3.88 (s, 3H), 4.05 (d, $^2J_{PH}$ = 20.1 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.20–7.30 (m, 10H), 7.64 ppm (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{PC}$ = 5.9 Hz), 16.4 (d, $^3J_{PC}$ = 5.9 Hz), 20.0, 20.1, 27.2, 34.9, 51.9, 55.6, 57.7 (d, $^1J_{PC}$ = 158.1 Hz), 57.9, 58.5 (d, $^3J_{PC}$ = 15.7 Hz), 62.6 (d, $^2J_{PC}$ = 7.3 Hz), 63.0 (d, $^2J_{PC}$ = 7.3 Hz), 69.9, 114.2, 126.6, 127.7, 127.8, 128.1, 128.3, 128.5, 128.7, 129.3, 129.4, 130.9, 135.2, 137.9, 162.8 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.70 ppm; MS (ESI): *m/z* 633.3 $[M+H]^+$; Anal. calcd for $C_{32}H_{45}N_2O_7PS$: C 60.74, H 7.17, N 4.43, found: C 60.79, H 7.24, N 4.35.

Diethyl benzo[*d*][1,3]dioxol-5-yl((2*S*,3*S*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)methylphosphonate (41a): Product was isolated as a 2:3 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (52%): R_f = 0.60 (EtOAc); IR ($CHCl_3$): $\tilde{\nu}$ = 3346, 3019, 1597, 1497, 1442, 1303, 1216, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H), 1.09–1.32 (m, 6H), 1.45–1.78 (m, 1H), 2.39–2.65 (m, 2H), 2.73–2.85 (m, 3H), 2.89–3.06 (m, 1H), 3.35–3.41 (m, 1H), 3.56–3.77 (m, 1H), 3.89 (s, 3H), 3.93–4.15 (m, 5H), 5.97 (s, 2H), 6.51–7.28 (m, 10H), 7.69 ppm (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (d, $^3J_{PC}$ = 5.9 Hz), 19.7, 20.0, 27.2, 36.1, 53.9, 55.6, 57.8 (d, $^1J_{PC}$ = 159.9 Hz), 58.2, 58.5 (d, $^3J_{PC}$ = 7.3 Hz), 62.9 (d, $^2J_{PC}$ = 7.3 Hz), 62.6 (d, $^2J_{PC}$ = 7.3 Hz), 69.5, 101.1, 108.0, 109.2 (d, $^3J_{PC}$ = 5.5 Hz), 114.2, 122.2 (d, $^3J_{PC}$ = 8.8 Hz), 126.5, 128.5, 129.4, 129.5, 129.7, 130.4, 138.0, 147.4, 147.7, 162.8 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.70 ppm; MS (ESI): *m/z* 677.6 $[M+H]^+$, 699.6 $[M+Na]^+$; Anal. calcd for $C_{33}H_{45}N_2O_9PS$: C 58.57c H 6.70, N 4.14, found: C 58.64, H 6.79, N 4.27.

Diethyl ((2*S*,3*S*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)(*p*-tolyl)methylphosphonate (41b): Product was isolated as a 3:2 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (78%): R_f = 0.65 (EtOAc); IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 3019, 1598, 1497, 1335, 1260, 1215, 1154 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.67 (d, *J* = 5.7 Hz, 3H), 0.71 (d, *J* = 5.7 Hz, 3H), 1.16–1.32 (m, 6H), 1.40–1.75 (m, 1H), 2.33 (s, 3H), 2.39–2.70 (m 2H), 2.76–2.87 (m, 3H), 2.94–3.11 (m, 1H), 3.28–3.39 (m, 1H), 3.50–3.70 (m, 1H), 3.88 (s, 3H), 3.83–4.20 (m, 5H), 6.91–7.26 (m, 11H), 7.67 ppm (d, *J* = 9.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.5 (d, $^3J_{PC}$ = 5.9 Hz), 19.7, 20.1, 21.2, 27.1, 36.1, 53.9, 55.6, 57.8 (d, $^1J_{PC}$ = 151.8 Hz), 58.1, 58.5, 58.8, 62.6 (d, $^2J_{PC}$ = 7.3 Hz), 63.0 (d, $^2J_{PC}$ = 7.3 Hz), 69.4, 114.2, 126.3, 128.2, 128.5, 128.9, 129.0, 129.2, 130.5, 132.6, 137.7, 138.8, 162.8 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.90 ppm; MS (ESI): *m/z* 669.6 $[M+Na]^+$; Anal. calcd for $C_{33}H_{47}N_2O_7PS$: C 61.28, H 7.32, N 4.33, found: C 61.39, H 7.47, N 4.26.

Diethyl ((2*S*,3*S*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)(4-nitrophenyl)methylphosphonate (41c): Product was isolated as a 3:2 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (56%): R_f = 0.56 (EtOAc); IR ($CHCl_3$): $\tilde{\nu}$ = 3463, 3019, 1597, 1523, 1348, 1260, 1216, 1155 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.69 (m, 6H), 1.05–1.35 (m, 6H), 1.54–1.85 (m, 1H), 2.26–2.69 (m, 2H), 2.75–2.88 (m, 3H), 2.91–3.03 (m, 1H), 3.26–3.44 (m, 1H), 3.57–3.83 (m, 1H), 3.89 (s, 3H), 3.93–4.25 (m, 4H), 4.30 (d, $^2J_{PH}$ = 21.3 Hz, 1H), 6.92–7.29 (m, 8H), 7.50–7.56 (m, 1H), 7.67 (d, *J* = 8.9 Hz, 2H), 8.17 ppm (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{PC}$ = 5.9 Hz), 16.5 (d, $^3J_{PC}$ = 5.9 Hz), 19.7, 20.0, 27.3, 36.5, 53.9, 55.7, 57.8 (d, $^1J_{PC}$ = 148.6 Hz), 58.5, 58.8, 63.0 (d, $^2J_{PC}$ = 6.9 Hz), 63.2 (d, $^2J_{PC}$ = 6.9 Hz), 69.5, 114.3, 123.4, 126.5, 128.6, 129.2, 129.4, 129.8, 130.0, 138.4, 143.9, 147.6, 163.0 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ = 21.85 ppm; MS (ESI): *m/z* 700.6 $[M+Na]^+$; Anal. calcd for $C_{32}H_{44}N_3O_9PS$: C 56.71, H 6.54, N 6.20, found: C 56.78, H 6.63, N 6.32.

Diethyl 1-((2*S*,3*S*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)-2-methylpropylphosphonate (41d): Product was isolated as a 1:1 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless

syrup (70%): $R_f = 0.35$ (EtOAc); IR ($CHCl_3$): $\tilde{\nu} = 3352$, 3019, 1598, 1497, 1335, 1259, 1216, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 0.63 (d, $J = 6.6$ Hz, 3H), 0.78 (d, $J = 6.6$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H), 1.04 (d, $^3J_{PH} = 6.8$ Hz, 3H), 1.30–1.40 (m, 6H), 1.69–1.74 (m, 1H), 2.07–2.23 (m, 1H), 2.68–2.71 (m, 1H), 2.82–2.89 (m, 2H), 2.94–3.07 (m, 2H), 3.12–3.22 (m, 2H), 3.32–3.35 (m, 1H), 3.54–3.59 (m, 1H), 3.88 (s, 3H), 4.09–4.20 (m, 4H), 6.96 (d, $J = 8.8$ Hz, 2H), 7.22–7.34 (m, 5H), 7.67 ppm (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 16.5$ (d, $^3J_{PC} = 5.5$ Hz), 17.7 (d, $^3J_{PC} = 2.2$ Hz), 18.3 (d, $^3J_{PC} = 2.5$ Hz), 19.9, 27.2, 29.4 (d, $^2J_{PC} = 3.6$ Hz), 38.0, 53.4, 55.6, 57.9, 58.4 (d, $^1J_{PC} = 158.9$ Hz), 60.5, 61.5 (d, $^2J_{PC} = 7.3$ Hz), 61.5 (d, $^2J_{PC} =$ 7.3 Hz), 67.8, 114.1, 126.4, 128.5, 129.3, 129.5, 130.7, 138.6, 162.7 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): $\delta = 28.52$ ppm; MS (ESI): m/z 621.5 $[M+Na]^+$; Anal. calcd for $C_{29}H_{47}N_{32}O_7PS$: C 58.17, H 7.91, N 4.68, found: C 58.31, H 8.09, N 4.59.

Diethyl ((2*S*,3*S*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylamino)(pyridin-2-yl)methylphosphonate (41e): Product was isolated as a 1:1 diastereomeric mixture; only peaks corresponding to the major isomer are given. Colorless syrup (63%): $R_f = 0.40$ (EtOAc); IR ($CHCl_3$): $\tilde{\nu} = 3379$, 3019, 2931, 1597, 1497, 1468, 1434, 1259, 1215, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.69$ (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H), 1.16 (t, $^3J_{PH} = 7.0$ Hz, 3H), 1.28 (t, $^3J_{PH} = 7.0$ Hz, 3H), 1.49–1.68 (m, 1H), 2.51–2.57 (m, 1H), 2.71–2.91 (m, 4H), 3.10–3.15 (m 1H), 3.40–3.45 (m, 1H), 3.59–3.64 (m, 1H), 3.89 (s, 3H), 3.78–4.11 (m, 4H), 4.45 (d, $^2J_{PH} = 22.1$ Hz, 1H), 6.98–7.00 (m, 2H), 7.10–7.23 (m, 5H), 7.44–7.54 (m, 3H), 7.77 (d, $J = 9.0$ Hz, 2H), 8.47 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.4$ (d, $^3J_{PC} = 5.9$ Hz), 19.9, 20.1, 27.2, 38.7, 53.7, 55.6, 58.1, 61.8 (d, $^1J_{PC} = 149.6$ Hz), 60.9, 62.7 (d, $^2J_{PC} = 7.3$ Hz), 62.8 (d, $^2J_{PC} = 7.3$ Hz), 70.1, 114.2, 122.5, 123.6, 126.2, 128.4, 129.3, 129.5, 130.7, 136.2, 138.3, 149.0, 155.7, 162.8 ppm; ^{31}P NMR (161 MHz, $CDCl_3$): $\delta = 22.40$ ppm; MS (ESI): m/z 656.5 $[M+Na]^+$; Anal. calcd for $C_{31}H_{44}N_3O_7PS$: C 58.75, H 7.00, N 6.63, found: C 58.68, H 7.12, N 6.49.

Diethyl (2*S*,3*R*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylphosphoramidate (15a): Colorless syrup (76%): $R_f = 0.50$ (EtOAc); $[\alpha]^{20}_D = +10.82$ ($c = 0.6$ in MeOH); IR ($CHCl_3$): $\tilde{\nu} = 3281$, 3020, 1689, 1604, 1542, 1497, 1456, 1395, 1335, 1262, 1215, 1155, 1046 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H), 1.14 (t, $^3J_{PH} = 7.1$ Hz, 3H), 1.18 (t, $^3J_{PH} = 7.1$ Hz, 3H), 1.81–1.95 (m, 1H), 2.85–2.94 (m, 3H), 3.08–3.16 (m, 2H), 3.26–3.51 (m, 3H), 3.75–3.88 (m, 4H), 3.86 (s, 3H), 4.22–4.30 (m, 1H), 6.97 (d, $J = 8.9$ Hz, 2H); 7.23–7.31 (m, 5H), 7.73 ppm (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 16.1$ (d, $^3J_{PC} = 7.3$ Hz), 16.2 (d, $^3J_{PC} = 7.3$ Hz), 20.0, 20.1, 27.1, 36.9 (d, $^3J_{PC} =$ 6.2 Hz), 52.9, 55.6, 56.6, 58.3, 62.2 (d, $^2J_{PC} = 5.8$ Hz), 62.5 (d, $^2J_{PC} =$ 5.8 Hz), 72.8 (d, $^3J_{PC} = 3.3$ Hz), 114.3, 126.4, 128.4, 129.4, 129.9, 130.4, 138.3, 162.9 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): $\delta = 8.22$ ppm; MS (ESI): m/z 543.6 $[M+H]^+$, 565.5 $[M+Na]^+$; Anal. calcd for $C_{25}H_{39}N_2O_7PS$: C 55.34, H 7.24, N 5.16, found: C 55.39, H 7.35, N 5.21.

Dibutyl (2*S*,3*R*)-3-hydroxy-4-(*N*-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-yl-phosphoramidate (15b): Colorless syrup (61%): $R_f = 0.70$ (EtOAc); $[\alpha]^{20}_D = +5.42$ ($c = 0.5$ in MeOH); IR ($CHCl_3$): $\tilde{\nu} = 3392$, 3019, 2963, 2874, 1597, 1578, 1497, 1456, 1391, 1337, 1260, 1216, 1154, 1092, 1030 cm^{-1} ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.78$–0.85 (m, 12H), 1.15–1.46 (m, 8H), 1.72–1.86 (m, 1H), 2.79–3.06 (m, 6H), 3.18–3.27 (m, 1H), 3.40–3.49 (m, 1H), 3.61–3.76 (m, 4H), 3.79 (s, 3H), 6.91 (d, $J = 8.9$ Hz, 2H); 7.13–7.23 (m, 5H), 7.65 ppm (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.6$, 18.7, 19.9, 20.2, 27.2, 32.2 (d, $^3J_{PC} = 2.2$ Hz), 32.4 (d, $^3J_{PC} = 2.2$ Hz), 37.2 (d, $^3J_{PC} = 5.5$ Hz), 53.1, 55.6, 56.4, 58.5, 66.1 (d, $^2J_{PC} = 7.3$ Hz), 66.2 (d, $^2J_{PC} = 7.3$ Hz), 72.7 (d, $^3J_{PC} = 3.7$ Hz), 114.3, 126.5, 128.4, 129.4, 129.9, 130.4, 138.0, 162.9 ppm; ^{31}P NMR (161 MHz, $CDCl_3$): $\delta = 8.26$ ppm; MS (ESI): m/z 621.5 $[M+Na]^+$; Anal. calcd for $C_{29}H_{47}N_2O_7PS$: C 58.17, H 7.91, N 4.68, found: C 58.29, H 8.05, N 4.61.

Biological assays

The anti-HIV activities and cytotoxicities of all the synthesized compounds were evaluated against wild-type HIV-1 (III_B), HIV-2 (ROD), and double mutant (RES056) strains in MT-4 cells using the 3-(4,5-dimethylthiazoldimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[26] Briefly, virus stocks were titrated in MT-4 cells and expressed as a 50% cell culture infective dose ($CCID_{50}$ values). MT-4 cells were suspended in culture medium at 1×10^5 cells mL^{-1} and infected with HIV at a multiplicity of infection of 0.02. Immediately after virus infection, 100 μL of the cell suspension was brought into each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. The test compounds were dissolved in DMSO at a concentration of 50 mM or higher. After 4-days incubation at 37 °C, the number of viable cells was determined using the MTT method. Compounds were tested in parallel for cytotoxic effects in uninfected MT-4 cells. The drugs currently being used in clinical treatment of HIV-1 infection, DDN/DDC and DMP266, were used as control.

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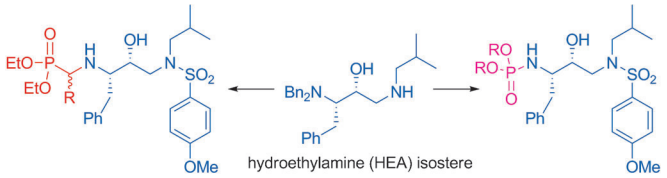
An Efficient Synthesis of a Hydroxyethylamine (HEA) Isostere and Its α-Aminophosphonate and Phosphoramidate Derivatives as Potential Anti-HIV Agents



Getting there faster: Efficient synthesis of a hydroxyethylamine (HEA) isostere was carried out with a one-pot reduction–transimination–reduction reaction sequence. α-Aminophosphonate and phosphoramidate derivatives of the HEA isostere were designed and synthesized. All of the synthesized α-aminophosphonate and phosphoramidate derivatives were assayed for their anti-HIV activities.

