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An Efficient and Practical Synthesis of the HIV Protease Inhibitor Atazanavir via a Highly Diastereoselective Reduction Approach

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Abstract:

An efficient and practical synthesis of the HIV-1 protease inhibitor Atazanavir was developed by employing the diastereoselective reduction of ketomethylene aza-dipeptide isostere 10 as the key and final step. The high diastereoselectivity of the amino ketone reduction by lithium tri-*tert*-butoxyaluminum hydride in diethyl ether to afford the desired *syn*-1,2-amino alcohol structure was achieved by Felkin−Anh control as a result of the bulky and chiral *N*-(methoxycarbonyl)-L-*tert*-leucinyl moiety as the nitrogen protecting group. The coupling of the two key intermediates, *N*-(methoxycarbonyl)-L-*tert*-leucine acylated benzyl hydrazine 7 and chloromethyl ketone 9, via an S_N2 reaction furnished the amino ketone 10 in high yield under our optimized conditions. Our new methodology features the late introduction of the *S*-hydroxyl group and the early acylation of benzyl hydrazine and chloromethyl ketone with *N*-(methoxycarbonyl)-L-*tert*-leucine, respectively, which confers high efficiency and easy purification.

Introduction

Atazanavir, trade name Reyataz (formerly known as BMS-232632), is an antiretroviral drug of the protease inhibitor (PI) class, approved by the FDA in June of 2003.[1,2] Like other antiretrovirals, it is used to treat infection of human immunodeficiency virus (HIV). Unlike most protease inhibitors, Atazanavir appears not to increase cholesterol, triglycerides, or blood sugar levels, which is a problem to various degrees with all other PIs.[3] Furthermore, the good oral bioavailability and favorable pharmacokinetic profile enables Atazanavir to be the first once-a-day protease inhibitor to treat AIDS.[4] This can provide a benefit for people seeking a simplified dosing regimen.

Atazanavir is an aza-peptidomimetic HIV-1 protease inhibitor, bearing an aza-dipeptide isostere structure (Figure 1). The focus of its synthesis is to construct the aza-dipeptide skeleton with desired stereochemistry. As outlined in Scheme 1, the original synthesis of Atazanavir was accomplished through the nucleophilic attack of the benzylhydrazine (**4**) on the (2*S*,3*R*)-epoxide (**2**), which was prepared from L-Boc-phenylalanine **1a**[5–8] or chiral diol **1b**.[9]

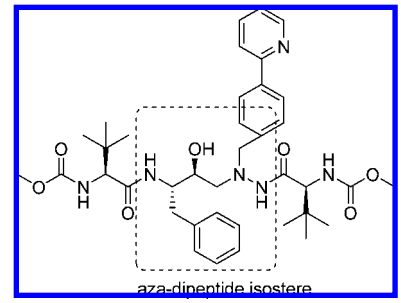

Figure 1. **Chemical structure of Atazanavir.**

The preparation of the key intermediate (2*S*,3*R*)-epoxide usually requires 3 or 4 steps of transformation starting from a chiral building block,[10] which endowed a higher cost and several limitations such as epimerization and problemic purification. On the other hand, the double coupling of the free amine of **5** with *N*-methoxycarbonyl-L-*tert*-leucine (Scheme 1) in the final step always was accompanied with low yield and isolation problems. So we tried to develop a concise and practical process to prepare Atazanavir. We herein report a more efficient and practical large-scale synthesis of the title compound by employing a convergent approach with a highly diastereoselective reduction as the key and last step.

New Strategy to Synthesize Atazanavir. As illustrated in Scheme 2, we designed a brand new strategy to synthesize Atazanavir. The distinct feature of our synthetic route is the late introduction of the (*S*)-hydroxyl group on the aza-dipeptide isostere structure via an asymmetric reduction in the final step. Correspondingly, the key amino ketone **10** was assembled from the fragments **7** and **9** via an S_N2 reaction. It is noteworthy that the early introduction of the *N*-methoxycarbonyl-L-*tert*-leucinyl moiety in the two fragments **7** and **9** is another feature of our

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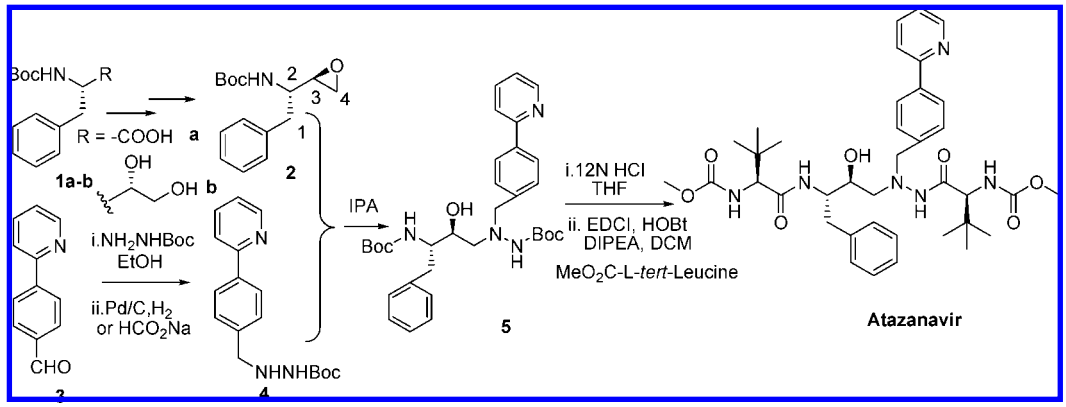
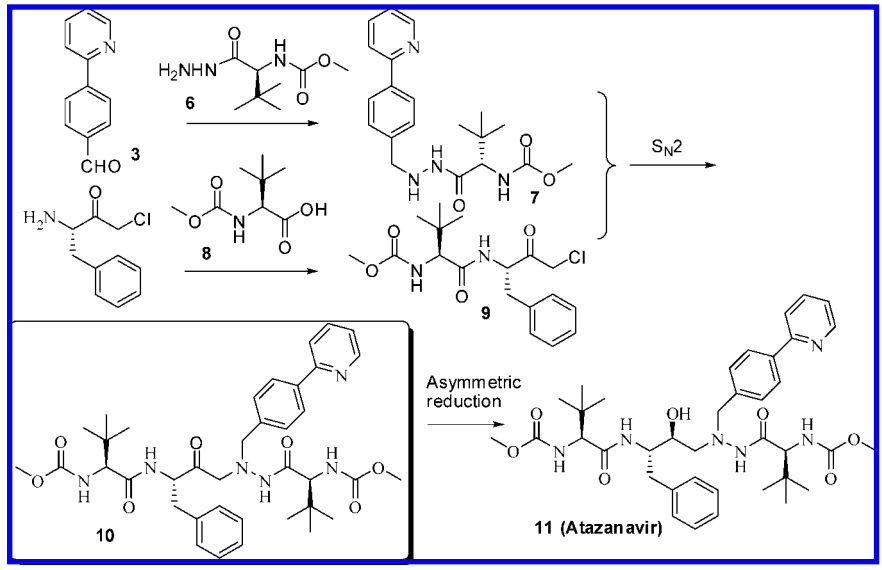
Scheme 1. **Literature-reported synthesis of Atazanavir via an epoxide opening approach**[8,9]



Scheme 2. **New strategy to synthesize Atazanavir by employing an asymmetric reduction as the key step**



strategy, in which the *N*-methoxycarbonyl-L-*tert*-leucinyl group acts as a protective group as well as the functional group, thus eliminating the need to protect and deprotect the amino functionality.

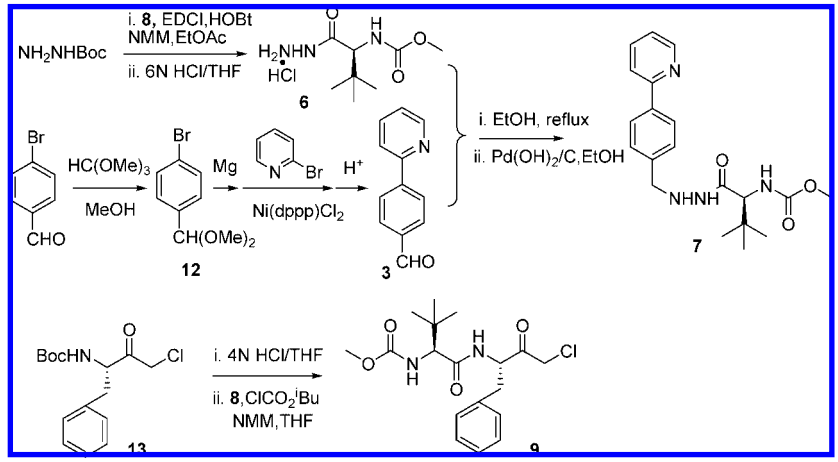
Results and Discussion

According to our designed synthetic route (Scheme 2), we started to synthesize Atazanavir via a more convergent approach. The two key intermediates, benzyl hydrazine **7** and chloromethyl ketone **9**, were prepared from pyridinyl benzaldehyde **3** and (*S*)-3-amino-1-chloro-4-phenylbutan-2-one, respectively.

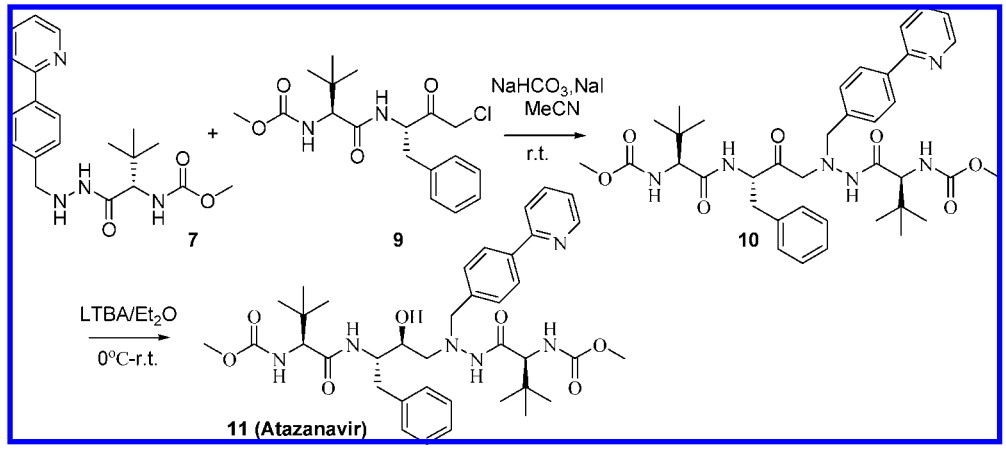
The union of **7** and **9** via an S_N2 reaction afforded the key precursor **10**, in which the base and solvent were optimized, with $NaHCO_3$ in CH_3CN being the best choice. An efficient procedure was developed for the diastereoselective reduction of the amino ketone into a *syn*-amino alcohol, which served as the key step of the synthesis of Atazanavir using our new strategy. The asymmetric reduction parameters such as reducing agent, solvent, and temperature were optimized for satisfying diastereoselectivty and yield for a large-scale synthesis. The bulky reductant lithium tri-*tert*-butoxyaluminum hydride (LTBA) in diethyl ether proved most effective to predominantly produce the desired *threo* amino alcohol via a Felkin−Anh control.

Synthesis of *N*-(Methoxycarbonyl)-L-*tert*-leucine Acylated Benzylhydrazine (7) and Chloromethyl Ketone (9). The synthesis of the *N*-(methoxycarbonyl)-L-*tert*-leucinyl benzylhydrazine (**7**) is shown in Scheme 3. Nickel(II)-catalyzed Kumada coupling of the Grignard reagent prepared from 4-bromobenzaldehyde dimethyl acetal (**12**) to 2-bromopyridine, followed by acidic hydrolysis, gave the corresponding 4-(pyridin-2-yl)-benzaldehyde (**3**).[8] The EDCI/HOBt-mediated coupling of *tert*-butyl carbazate with *N*-(methoxycarbonyl)-L-*tert*-leucine (**8**) followed by treatment with 6 N HCl furnished another building block **6** in 95% yield. The subsequent condensation of the aldehyde (**12**) with *N*-(methoxycarbonyl)-L-*tert*-leucinyl hydrazine (**6**) was carried out in hot ethanol. The resulting mixture was subjected to the next reaction without further purification. In general, the hydrazone can be converted into the corresponding hydrazine by hydrogenation or reduction with borohydride reagents. However, in our case, the hydrogenation under the original conditions (Pd/C, MeOH, and 1 atm H_2)[5,6] required 3 days to be completed. Replacement of Pd/C with Raney Ni resulted in a more sluggish reaction. Chemical reduction using $NaBH_4$ or $NaHB(OAc)_3$ led to product mixtures with only 30−40% yield of compound **7**. We examined the more active catalyst of $Pd(OH)_2/C$ in ethanol, and to our delight, the hydrogenation proceeded quantitatively under 1 atm H_2 in 12 h. Recrystallization from *i*PrOH−EtOH furnished the desired

Scheme 3. **Synthesis of key intermediates benzylhydrazine (7) and chloromethyl ketone (9)**



Scheme 4. **Synthesis of Atazanavir**



N-(methoxycarbonyl)-L-*tert*-leucinyl benzylhydrazine **7** in an overall isolated yield of 78% with ~100 area % (AP).

Another key intermediate **9** was synthesized conveniently. As indicated in Scheme 3, the acidic treatment of (*S*)-*tert*-butyl 4-chloro-3-oxo-1-phenylbutan-2-ylcarbamate (**13**) followed by acylation with *N*-(methoxycarbonyl)-L-*tert*-leucine (**8**) via a mixed anhydride method afforded the *N*-(methoxycarbonyl)-L-*tert*-leucinyl chloromethyl ketone (**9**) in 72% overall isolated yield with 98 AP through recrystallization from petroleum ether and ethyl acetate. No epimerization was observed under our reaction conditions. The *N*-protected α-amino chloromethyl ketone **13** can be prepared conveniently from L-phenylalanine in a one-pot three-step sequence through a mixed anhydride and diazoketone intermediates,[11] but for large-scale synthesis, the starting material **13** was purchased from Desano Company in Shanghai.

Development of the Diastereoselective Reduction of Amino Ketone to the *syn*-Amino Alcohol and Synthesis of Atazanavir. With the two key intermediates **7** and **9** in hand, we turned to the synthesis of Atazanavir via a convergent route as depicted in Scheme 4.

The coupling reaction between **7** and **9** was investigated first. As indicated in Table 1, the reaction conditions were optimized in terms of the base, solvent, and temperature. We found that the S_N2 reaction performed in DMF with K_2CO_3/NaI or in acetone with $NaHCO_3$/NaI at 50 °C only gave 30% and 50% yield, respectively. Raising the temperature to 60 °C resulted in a worse conversion, producing less than 10% yield of the desired compound **10**. Because amino acid derived chloromethyl ketones readily undergo a general dehydrohalogenation reaction under mild, basic, non-nucleophilic conditions to afford α,β-unsaturated ketones,[12] we supposed that the dipeptidyl chloromethyl ketone **9** might undergo a similar transformation to give unsaturated ketones as the major product under the high temperature and basic conditions. So, a mild condition for the S_N2 reaction was investigated by lowering the reaction temperature and using the weaker base of $NaHCO_3$ in DMF. As we expected, the optimized condition of $NaHCO_3$/NaI in DMF at room temperature readily provided a clean reaction, but the difficult disposal of DMF solvent renders this method unattractive. We examined MeCN as the solvent and $NaHCO_3$ as the base with catalytic NaI, and a complete coupling could be achieved reliably in 12 h at room temperature. Facile workup to remove unreacted **7** with $KHSO_4$ aqueous solution furnished compound **10** in yield of 96% with 92 AP.

The final and key step was how to install the *S*-hydroxyl group in the aza-dipeptide isostere portion. In general, the hydroxyl group of the amino alcohol is installed either by the addition of an organometallic reagent to an amino aldehyde or

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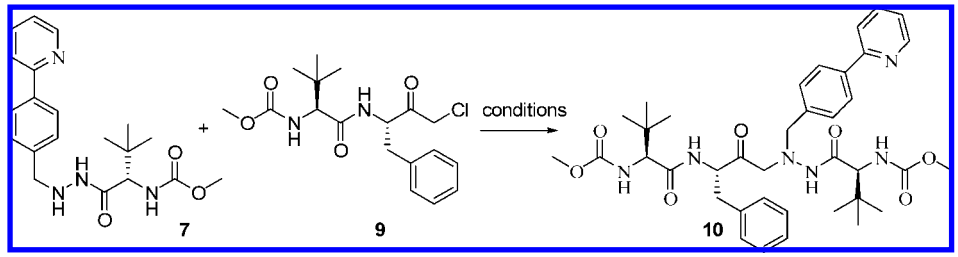
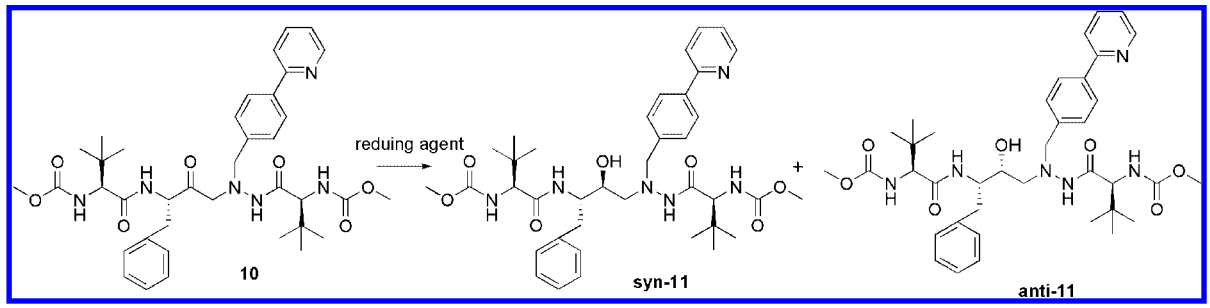
Table 1. **Coupling of *N*-(methoxycarbonyl)-L-*tert*-leucinyl-protected benzylhydrazine 7 and chloromethyl ketone 9 under various conditions**



entry	base	*T* (°C)	solvent	conversion yield
1	K_2CO_3, NaI	50	DMF	30%
2	$NaHCO_3$, NaI	50	acetone	50%
3	$NaHCO_3$, NaI	60	DMF	<10%
4	$NaHCO_3$, NaI	rt	DMF	>90%
5	$NaHCO_3$, NaI	rt	MeCN	quant

Table 2. **Reduction of *N*-(methoxycarbonyl)-L-*tert*-leucinyl protected amino ketone 10 with various reducing agents/conditions**



entry	reducing agent	conditions	*syn*:*anti*[a]
1	$NaBH_4$	MeOH, 0 °C	3:2
2	$Zn(BH_4)_2$	THF, 0 °C	3:1
3	$LiAlH(O^tBu)_3$	THF, 0 °C	4:1
4	$LiAlH(O^tBu)_3$	Et_2O, 0 °C	28:1

[a] The *syn*:*anti* ratio was determined on the crude product with HPLC.

by the reduction of an amino ketone. The reduction of *N*-protected amino ketones can be carried out stereoselectively to produce either the *syn*- or *anti*-amino alcohol diastereomer, depending on the mode of stereocontrol.[13] Basically, *N*-carbamate protected amino ketone is reduced selectively to *anti*-amino alcohols via chelation control, while the *N*,*N*-dibenzyl or *N*-trityl protecting group renders the amino group sufficiently bulky to achieve Felkin−Anh control and thus produce *syn*-amino alcohols.[13,14] It is clear that the nitrogen protecting group is an important stereocontrol element.

In our case, the nitrogen of the amino ketone **10** is acylated with (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid, which functions as a bulky protecting group. So we assumed that the reduction of our compound **10** would achieve Felkin−Anh control to produce the *syn*-amino alcohol as the major product.

A first attempt was made with the borohydride reducing agents in hydroxylic or aprotic solvents (Table 2). To our delight, the reduction of amino ketone **10** with sodium borohydride in methanol or with zinc borohydrides in THF gave the *syn*-amino alcohol **11** as major product (Felkin−Anh control), but only poor stereoselectivities of 3:2 and 3:1 (*syn*:*anti* ratio), respectively, were obtained. The stereochemical outcome in different solvents here was consistent with published findings.[13–16] Usually, hydroxylic solvents (MeOH and other alcohols) promote the exchange and/or disproportionation of ligands attached to boron or aluminum so that the substrate can become bound to boron or aluminum in the chelated fashion needed for effective chelation stereocontrol (vide infra).[13,16] Consequently borohydride or aluminum hydride reagents in alcohol solvents give chelation-control reduction, whereas the nonhydroxylic solvents facilitate a Felkin−Anh controlled reduction. In our study, the combination of zinc borohydrides in THF really provides a better *syn*-selectivity than the reducing system of sodium borohydride in methanol.

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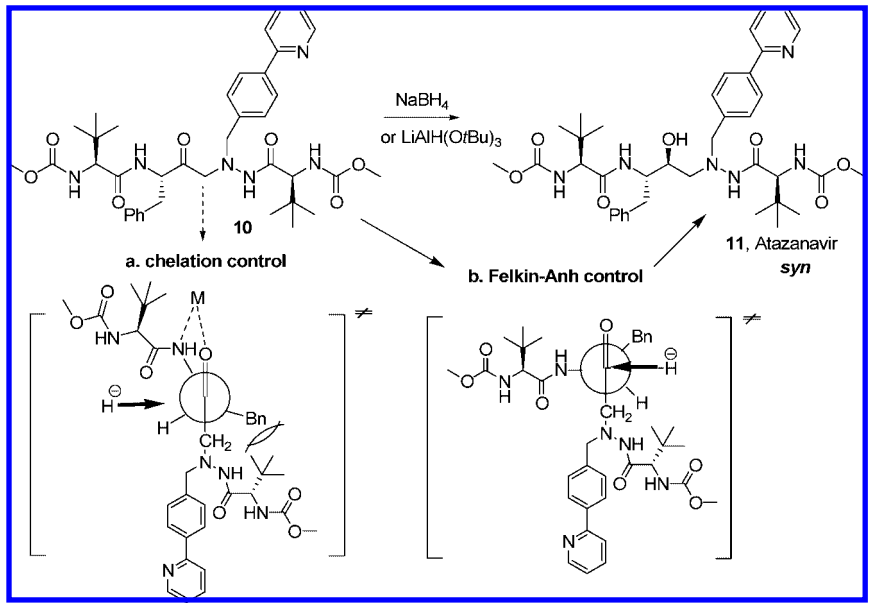

Figure 2. **Transition state of the reduction.**

On the other hand, since the steric hindrance endowed by the amino ketone or the reducing agents appears to favor achieving Felkin−Anh control, the use of a more bulky and more reactive reductant of $LiAlH(O^tBu)_3$ in THF at 0 °C resulted in an obvious increase of the *syn*:*anti* ratio (4:1). Similar stereoselectivity was reported in Hoffman's work,[13] in which *N*-trityl-protected amino ketones could be reduced selectively to *syn*-amino alcohols with $LiAlH(O^tBu)_3$ in THF at −5 °C. Considering that solvent effect is an important factor to influence the stereoselectivity,[13–16] we examined $LiAlH(O^tBu)_3$ in Et_2O with the aim to increase the *syn* diastereoselectivity further. The choice of Et_2O was inspired by a literature-reported successful use of $LiAlH(O^tBu)_3$ in Et_2O to achieve the *threo* selective reduction of the halomethyl ketones.[10] Also in Hoffman's work, it was observed that when changing solvent from THF to ether in the reduction of *N*-carbamate-protected amino ketones by $Zn(BH_4)_2$, the stereoselectivity was switched from 2:1 to 1:2 (*anti*:*syn*).[13] Encouragingly, in our work, clean reaction and excellent *syn*-selectivity (28:1) was obtained under very mild conditions (ice bath, reaction time of 4 h) when employing $LiAlH(O^tBu)_3$ in Et_2O as the reagent−solvent combination. This reduction procedure was scaled up to afford 39 g of Atazanavir **11** with 99.4 AP. The reason why diethyl ether is a preferred solvent for the Felkin−Anh control reduction of our substrate over THF is not clear, but this reagent−solvent combination might be useful for the synthesis of other protease inhibitors containing a *syn*-amino alcohol core structure.

It is worthwhile to note that the construction of the *syn*-vicinal amino alcohol via amino ketone reduction in our approach was achieved directly on the aza-dipeptide isostere structure, devoid of any protecting group exchanging. The *N*-(methoxycarbonyl)-L-*tert*-leucinyl group played a dual role in our route: on the one hand, it is the structural element of the molecule; on the other hand, it serves as the protecting group that is bulky enough to enforce the Felkin−Anh control. This is the distinct advantage over the previously reported synthesis of hydroxyethylene dipeptide isosteres.[17]

Mode of Stereocontrol in the Amino Ketone Reduction. Examination of the literature revealed that high *syn*-selectivity was achieved only in the case of *N*,*N*-dibenzyl-,[14] *N*-trityl-,[13] or *N*-phthaloyl-protected[18] amino ketones. Our study provided the first example that *N*-L-*tert*-leucinyl-protected amino ketone was reduced by the new reagent−solvent combination of $LiAlH(O\text{-}^tBu)_3$ in diethyl ether to exclusively give the *syn*-1,2-amino alcohol, which achieved a good Felkin−Anh stereocontrol.

Principally, to achieve Felkin−Anh control in the reduction of protected amino ketones and thus produce *syn*-amino alcohols, the amine group must be modified to make it sterically bulky. This renders a steric preference for a Felkin−Anh transition state and minimizes effective chelation involving the amino nitrogen and the ketone oxygen.[13] According to the principal, we proposed a transition state of the reduction of our substrate **10**, as demonstrated in Figure 2. The *N*-(methoxycarbonyl)-L-*tert*-leucinyl group installed on the nitrogen of the amino ketone confers a steric congestion with benzyl group. In order to stay a low energy conformation, the ketone **10** preferentially adopts a Felkin−Anh transition state, leading to a high *syn*-stereoselectivity.

As a comparison study, we examined the stereoselectivity of the reduction of *N*-carbamate-protected aza-dipeptide isostere. As shown in Scheme 5, *N*-Boc-protected amino ketone (**14**) was reduced by $NaBH_4$in MeOH or $Zn(BH_4)_2$in THF to give *anti*-1,2-amino alcohols (**15**) as the major product, with an *anti*:*syn* ratio of 3:2 and >20:1, respectively. The reduction proceeded via a chelation control predominantly. This result is in agreement with the reported general amino ketone reduction protocol.

Conclusions

In conclusion, we have successfully developed an efficient and convenient route toward the synthesis of HIV protease

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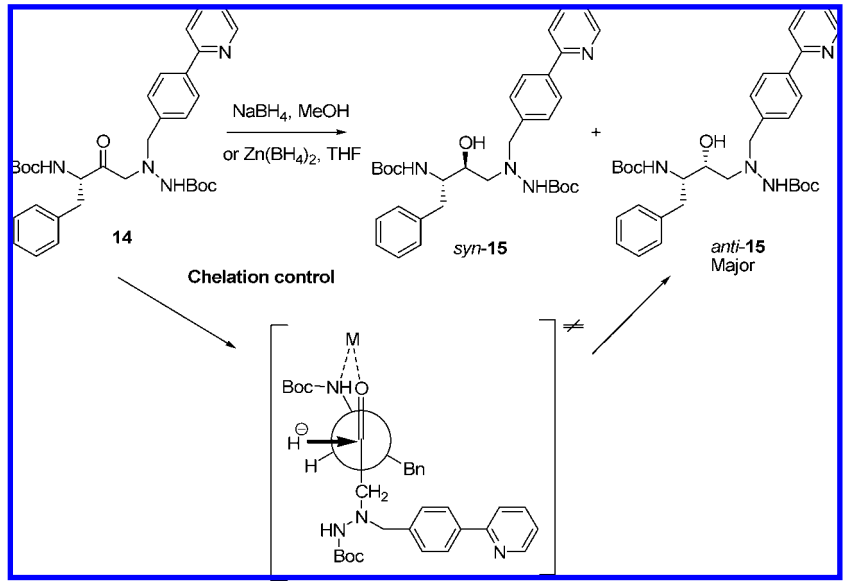
Scheme 5. **Reduction of the *N*-carbamate-protected aza-dipeptide isostere**



inhibitor Atazanavir. Distinct from literature-reported procedures, our new approach employed the amino ketone reduction of aza-dipeptide isostere with a new reagent−solvent combination of $LiAlH(O^tBu)_3$ in Et_2O as the key and final step, which achieved Felkin−Anh stereocontrol to offer the desired *syn*-1,2-amino alcohol exclusively. Furthermore, the *N*-(methoxycarbonyl)-L-*tert*-leucinyl group played a dual role in our convergent route: on the one hand, it is the structural element of the molecule, and on the other hand, it serves as the protecting group of the two fragments of benzylhydrazine and chloromethyl ketone. The new strategy offers an alternative and efficient approach to prepare hydroxyethylene aza-dipeptide isostere with high diastereoselectivity and good yield.

Experimental Section

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. Melting points are uncorrected. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (100 MHz) were recorded in $CDCl_3$. Specific rotations (uncorrected) were determined in a Perkin-Elmer 241 polarimeter. Low and high resolution mass spectra were determined on a MAT-95 mass spectrometer. HPLC analysis results are described as area % (AP).

***N*-1-[*N*-(Methoxycarbonyl)-L-*tert*-leucinyl]-*N*-2-[4-(pyridine-2-yl)-benzyl] Hydrazine (7).** To the solution of **6**(31.65 g, 132.1 mmol) in EtOH (250 mL) was added triethylamine (21.9 mL, 158.5 mmol) at room temperature under N_2. After 1 h of stirring at room temperature, a solution of **3** (24.18 g, 132.1 mmol) in EtOH (100 mL) was added. The mixture was heated to reflux for 4 h, then cooled to room temperature, treated with $Pd(OH)_2$ (5 g), and stirred under 1 atm H_2 at room temperature for 12 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give an oily residue that was recrystallized from isopropyl ether/ethanol to yield **7** as a white solid (37 g, 75.7% yield, 100.0 AP). Mp: 134–135 °C; $[\alpha]^{20}_D = -22.5°$ (c = 0.91, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (d, 1H, J = 4.5 Hz), 7.99 (d, 2H, J = 8.4 Hz), 7.85–7.75 (m, 2H), 7.48 (d, 2H, J = 8.4 Hz), 7.30 (m, 1H), 5.38 (d, 1H, J = 9.6 Hz), 4.05 (q_{AB}, 2H, J = 12.6 Hz, 16.8 Hz), 3.78 (d, 1H, J = 9.6 Hz), 3.67 (s, 3H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 157.1, 157.0, 149.6, 138.6, 138.2, 136.7, 129.2 × 2, 126.9 × 2, 122.1, 120.4, 61.1, 55.5, 52.3, 34.5, 26.4 × 3. MS (EI): m/z 370 $(M)^+$. HRMS (EI): calcd for $C_{20}H_{26}O_3N_4$ (M^+) 370.2005, found 370.2011.

Methyl (*S*)-1-((*S*)-4-Chloro-3-oxo-1-phenylbutan-2-ylcarbamoyl)-2,2-dimethylpropyl Carbamate (9). To a solution of *tert*-butyl (*S*)-4-chloro-3-oxo-1-phenylbutan-2-ylcarbamate (38.2 g, 128.3 mmol) in dry THF (100 mL) was added 4 N HCl (100 mL). The mixture was stirred for 4 h at 50 °C and concentrated to remove the THF, and the residue was washed with dichloromethane (40 mL) three times. The aqueous layer was concentrated to give a white solid. To a cold solution of **8** (26.4 g, 140 mmol) in dry THF (350 mL) was added NMM (28 mL, 256 mmol) followed by careful addition of isobutyl chloroformate (18.44 mL, 128 mmol). After stirring for 20 min at –25 °C, the above white solid was added to the solution. The reaction mixture was stirred for 1 h at −20 °C and for 1–3 additional hours at room temperature. The solvent was removed in vacuum, and the residue was taken up in ethyl acetate. The usual workup to give an oily residue, crystallized from petroleum ether/ ethyl acetate to afford **9** as a white solid (33.8 g, 71.9% yield, 97.9 AP). Mp: 115–116 °C. $[\alpha]^{20}_D = -3.9°$(c = 0.92, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.35 (m, 3H), 7.16 (d, 2H, J = 6.6 Hz), 6.23 (d, 1H, J = 6.0 Hz), 5.27 (d, 1H, J = 9.3 Hz), 4.93–5.01 (m, 1H), 4.14 (d, 1H, J = 15.6 Hz), 3.85–3.94 (m, 2H), 3.68 (s, 3H), 3.01–3.02 (m, 2H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 170.8, 157.0, 135.1, 129.0 × 2, 128.9 × 2, 127.5, 62.5, 57.1, 52.4, 47.7, 37.5, 34.4, 26.4 × 3. MS (EI): m/z 368 (M^+). HRMS (EI): calcd for $C_{18}H_{25}ClN_2O_4$ (M^+) 368.1503, found 368.1517.

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4-oxo-6-phenyl-2-azahexane (10). To a solution of **9** (28 g, 76 mmol) in MeCN (250 mL) was added NaI (12.4 g, 83 mmol). The mixture was stirred for 15 min at room temperature, and a solution of **7** (30.7 g, 83 mmol) in MeCN (350 mL) was added. The reaction mixture was stirred for another 15 min and treated with $NaHCO_3$ (12.7 g, 152 mmol). The mixture was stirred for 12 h and concentrated under reduced pressure to remove the MeCN. The residue was diluted with ethyl acetate (500 mL), and the organic phase was washed with $KHSO_4$ and brine, dried over Na_2SO_4, and concentrated in vacuum to give crude product **10** (51 g, 96.2% yield, 91.7 AP) as a yellow solid that was directly used for the next step without further purification. $[\alpha]^{22}_D = +3°$ ($c = 0.15$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (d, 1H, $J = 5.1$ Hz), 7.98–7.88 (m, 3H), 7.74–7.64 (m, 2H,), 7.42 (d, 2H, $J = 8.1$ Hz), 7.22–7.16 (m, 3H), 7.07 (d, 2H, $J = 7.2$ Hz), 5.69 (d, 1H, $J = 9.0$ Hz), 5.51 (d, 1H, $J = 10.2$ Hz), 4.80 (d, 1H, $J = 6.0$ Hz), 4.20–4.07 (m, 3H), 3.82 (d, 1H, $J = 17.4$ Hz), 3.75 (d, 1H, $J = 9.6$ Hz), 3.64 (s, 3H), 3.59 (s, 3H), 3.04–2.86 (m, 2H), 0.94 (s, 9H), 0.80 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 173.1, 170.8, 169.8 × 2, 157.0, 149.6, 138.8, 137.3, 136.7, 135.6, 129.5 × 2, 129.0 × 2, 128.8 × 2, 127.2 × 2, 126.9, 122.1, 120.4, 62.4, 61.2, 60.2, 59.9, 57.7, 52.3, 36.9, 34.5, 34.3, 26.4 × 3, 26.3 × 3. MS (ESI): *m*/*z* 703.6 $(M + 1)^+$, 725.6 $(M + Na)^+$. HRMS (ESI): calcd for $C_{38}H_{50}N_6O_7Na$ $(M + Na)^+$ 725.3639, found 725.3615.

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (11, Atazanavir). To the solution of **10** (24.57 g, 35.0 mmol) in diethyl ether (400 mL) was added LTBA (20.83 g, 87.5 mmol) at 0 °C. The mixture was stirred for 4 h at 0 °C and then quenched with water (2 mL). The solvent was removed in vacuum, and the residue was taken up in dichloromethane (200 mL) and washed with brine. The organic layer was concentrated to provide a yellow solid that was treated with 370 mL of isopropyl ether−EtOH solution and heated until reflux was observed. The slurry was cooled to room temperature, and the solid was collected by filtration, washed with 100 mL of cool isopropyl ether−EtOH solution, and dried at 50 °C under vacuum to give 18 g of crude free base. The combined crude product (46 g) was recrystallized from the mixture solvent of ethanol–water twice to afford Atazanavir (39 g, 62%, AP 99.4) as a white solid. Mp: 198–200 °C, $[\alpha]^{20}_D = -44.3°$ ($c = 0.9$, EtOH) [lit.[8] $[\alpha]^{20}_D = -47°$ ($c = 1.0$, EtOH)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (d, 1H, $J = 0.8$ Hz), 7.89–7.80 (m, 4H), 7.51 (d, 1H, $J = 8.4$ Hz), 7.37–7.32 (m, 1H), 7.23–7.17 (m, 4H), 7.15–7.10 (m, 1H), 4.14 (t, 1H, $J = 7.2$ Hz), 3.99 (s, 2H), 3.84 (s, 1H), 3.75 (d, 1H, $J = 9.6$ Hz), 3.68 (s, 1H), 3.63 (s, 3H), 3.59 (s, 3H), 2.96–2.82 (m, 3H), 2.69 (d, 1H, $J = 12.9$ Hz), 0.82 (s, 9H), 0.71 (s, 9H). MS (EI): *m*/*z* 704 $(M)^+$. Anal. Calcd for $C_{38}H_{52}N_6O_7$: C, 64.75; H, 7.44; N, 11.92. Found: C, 64.41; H, 7.33; N, 11.69.

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Supporting Information Available

The synthesis for the known compounds **3**, **6**, **8**, and **12**; analytical data for new compounds; ^{1}H NMR spectra for compounds **3**, *N*-Boc-**6**, and **7**–**11** and ^{13}C NMR spectra for compounds **7**, **9**, and **10**; HPLC chart for the purity identification of compounds **7**, **9**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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