PRACTICAL SYNTHESIS OF (2*S*,3*S*)-3-AMINO-2-HYDROXY-4-PHENYLBUTYRIC ACID, A KEY COMPONENT OF HIV PROTEASE INHIBITORS

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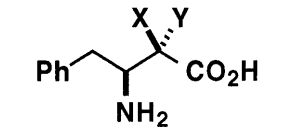
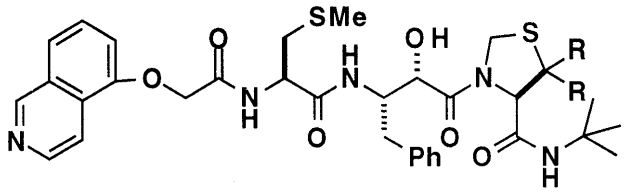
Synthesis of (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid was achieved by the highly diastereoselective cyanohydrin formation of (*S*)-2-*N*,*N*-dibenzylamino-3-phenylpropanal with acetone cyanohydrin in the presence of trimethylaluminum as a key step.

Key words KNI-227; HIV protease inhibitor; 3-amino-2-hydroxy-4-phenylbutyric acid; acetone cyanohydrin; diastereoselective reaction

(2*S*,3*S*)-3-Amino-2-hydroxy-4-phenylbutyric acid [(2*S*,3*S*)-**1**] known as (2*S*,3*S*)- or (-)-allophenylnorstatine, is a key component of the promising HIV protease inhibitors KNI-227[1] and KNI-272,[1] which have been designed based on the transition state mimetic concept. As a part of our research program directed at exploring practical synthetic routes for peptide mimetics such as renin inhibitor and bestatin,[2] we recently reported an expeditious synthesis of the key building block of the HIV protease inhibitor VX-478.[3] As an extension of these synthetic studies, we wish to report here a practical synthetic method of (2*S*,3*S*)-**1** explored using the highly diastereoselective cyanohydrin formation.



(2*S*,3*S*)-**1**: X=H, Y=OH
(2*R*,3*S*)-**1**: X=OH, Y=H



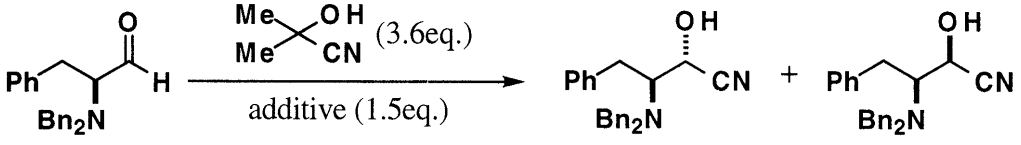
KNI-227: R=Me
KNI-272: R=H

Previously, we developed an efficient synthetic method of (2*R*,3*S*)-**1** which employs the diastereoselective formation of (2*R*,3*S*)-cyanohydrin acetate from an α-aminoaldehyde with sodium cyanide under phase-transfer conditions.[2a,b] This method, however, was found to be useless for synthesizing the corresponding (2*S*,3*S*)-isomer.[2a,b,4,5] Although (2*S*,3*S*)-cyanohydrin has been obtained diastereoselectively by cyanosilylation of an α-aminoaldehyde mediated by Lewis acids,[6] this method seems to lack practicality because of the use of expensive trimethylsilyl cyanide. In order to produce (2*S*,3*S*)-**1** more efficiently, a novel method was sought which can effectively introduce a nitrile moiety into an α-aminoaldehyde in a highly diastereoselective manner. Incidentally, acetone cyanohydrin was widely utilized as an alternative reagent for cyanohydrin formation.[7] We have now found that the reaction of acetone cyanohydrin with an α-aminoaldehyde proceeds in a highly stereoselective manner in the presence of alkylaluminum reagents,[7] affording the corresponding (2*S*,3*S*)-cyanohydrin as a major product. The (2*S*,3*S*)-cyanohydrin separated in a pure state was readily derived to (2*S*,3*S*)-**1** in two steps.

First, we examined the reactions of (*S*)-2-*N*,*N*-dibenzylamino-3-phenylpropanal (**2**)[6] with

acetone cyanohydrin in the presence of various additives such as alkylaluminums, titanium isopropoxide, zinc chloride, and potassium carbonate. The results summarized in Table 1 show that the use of alkylaluminums, especially trimethylaluminum and dichloroethylaluminum, afford the best results.[8] Thus, when **2** was allowed to react with acetone cyanohydrin in the presence of trimethylaluminum at 0°C, (2*S*,3*S*)-**3** was found to be produced in quantitative yield with high diastereoselectivity [(2*S*,3*S*)-**3**:(2*R*,3*S*)-**3**=5.3:1] (run 5). The desired (2*S*,3*S*)-diastereoselectivity could be improved to 13:1 by reaction at -15°C with slightly decreased chemical yield (75%) (run 6). The optical integrity of separated (2*S*,3*S*)-**3** was examined by converting to the corresponding (*R*)- and (*S*)-Mosher esters by treatment with (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) in pyridine, respectively. Neither of the diastereomers was detected in the 400 MHz ^{1}H-NMR spectra of the Mosher esters, establishing that (2*S*,3*S*)-**3** was obtained as a pure enantiomer.

Table 1. Diastereoselective Reactions of Acetone Cyanohydrin with α-Aminoaldehyde 2

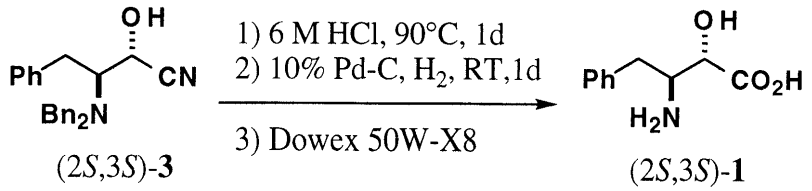


2 (2*S*,3*S*)-**3** (2*R*,3*S*)-**3**

Run	Additive	Conditions	Yield (%)	Ratio of (2*S*,3*S*)-**3** : (2*R*,3*S*)-**3**[a]
1	$Ti(i\text{-}PrO)_4$	RT, 48h	92	3.4 : 1
2	$ZnCl_2$	RT, 18h	43	3 : 1
3	K_2CO_3[b]	RT, 5h	91	1 : 1
4	DIBAL-H	0°C, 1h	94	3 : 1
5	Me_3Al	0°C, 7h	100	5.3 : 1
6	Me_3Al	-15°C, 72h	75	13 : 1
7	iBu_3Al	0°C, 3h	82	3 : 1
8	$EtCl_2Al$	RT, 6h	70	9 : 1

a) The ratio was determined by 400 MHz ^{1}H-NMR spectra. *b)* The reaction was carried out in MeOH saturated with K_2CO_3.

With a pure sample of (2*S*,3*S*)-**3** in hand, the preparation of (2*S*,3*S*)-**1** was next attempted. Thus, hydrolysis of (2*S*,3*S*)-**3** by heating in 6 M HCl followed by hydrogenolysis over 10% Pd-C and treatment with ion-exchange resin (Dowex 50W-X8, H^+-form) gave rise to (2*S*,3*S*)-**1** [mp 228-233°C (decomp.), $[\alpha]_D^{20}$ -5.4°(*c* 0.37, 1N HCl); lit.[9] $[\alpha]_D^{20}$ -5.4°(*c* 0.51, 1M HCl)] in 64% overall



(2*S*,3*S*)-**3** (2*S*,3*S*)-**1**

yield.

As described above, we have succeeded in developing a practical synthetic route for (2*S*,3*S*)-**1** by using the diastereoselective cyanohydrin formation with acetone cyanohydrin. Taking into account its directness and operational simplicity, the overall process reported here may serve as one of the most practical synthetic methods for (2*S*,3*S*)-**1**.

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References and Notes

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8) General procedure for the cyanohydrin formation: A solution of trimethylaluminum in hexane (0.99 M, 0.230 ml, 0.228 mmol) was added to a mixture of acetone cyanohydrin (0.050 ml, 0.547 mmol) and (*S*)-2-*N*,*N*-dibenzylamino-3-phenylpropanal (49.9 mg, 0.152 mmol) in CH_2Cl_2 (1 ml) at 0°C under an argon atmosphere. After stirring for 7 h at the same temperature, a saturated ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with AcOEt. The organic phase was washed with brine, dried over anhyd. Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel (AcOEt:hexane =1:9) to give a mixture of (2*S*,3*S*)- and (2*R*,3*S*)-**3** [54.1 mg, 100%; (2*S*,3*S*)-**3**:(2*R*,3*S*)-**3**=5.3:1 (determined by 400 MHz ^{1}H-NMR spectrum)]. Each isomer was separated by recrystallization from CH_2Cl_2/hexane or preparative TLC (CH_2Cl_2:hexane=1:1). (2*S*,3*S*)-**3**: mp 98°C (CH_2Cl_2/hexane). $[\alpha]_D^{20}$=+49.4° (*c* 1.01, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.95 (1H, dd, *J*=10.5, 13.2Hz, CH_2Ph), 3.21-3.26 (1H, m, CHN), 3.30 (1H, dd, *J*=4.5, 13.2Hz, CH_2Ph), 3.53, 4.22 (4H, AB-q, *J*=13.2Hz, Bn), 3.99 (1H, dd, *J*=5.5, 8.5Hz, CHOH), 4.46 (1H, d, *J*=8.5Hz, OH), 7.26 (15H, m, ArH). MS *m/z*: 357 (MH^+). *Anal.* Calcd. for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 81.10; H, 6.98; N, 7.81. (2*R*,3*S*)-**3**: colorless oil. $[\alpha]_D^{20}$=+47.9° (*c* 1.05, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.99 (1H, dd, *J*=5.8, 14.1Hz, CH_2Ph), 3.12 (1H, dd, *J*=8, 14.1Hz, CH_2Ph), 3.33 (1H, ddd, *J*=5.8, 8, 8.5Hz, CHN), 3.46, 3.85 (4H, AB-q, *J*=13.2Hz, Bn), 3.89 (1H, brs, OH), 4.26 (1H, d, *J*=8.5Hz, CHOH), 7.26 (15H, m, ArH). MS *m/z*: 357 (MH^+).
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