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Diastereoselective synthesis of a core fragment of ritonavir and lopinavir

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ABSTRACT

A novel approach to the synthesis of Boc-core, a key starting material for ritonavir and lopinavir involving an unprecedented diastereoselective nitroaldol reaction on β-amino aldehyde is disclosed.

A key element present in many HIV protease inhibitors for example, ritonavir and lopinavir (Fig. 1) contains a chiral 1,4-diamino-3-hydroxy architecture.[1] In general, stereoselective manipulation at two stereogenic centers, in the presence of a systemic predisposed chirality, in a convergent fashion imposes a formidable challenge. The direct nitroaldol reaction between protected amino alcohol and aldehyde is recognized as an economical means to construct chiral C–C bond.[2] However, despite the proven potential, so far, apart from the methodology disclosed by Piantner et al.[2a] that employs nitromethane, there is no precedence of asymmetric version describing the reaction of an enantiopure protected β-amino aldehyde with a substituted nitroalkane derivative in order to access 1,4-diamino-3-hydroxy framework. In particular, the development of a catalyst-controlled highly diastereselective nitroaldol reaction yielding a key component of the biologically active molecules presents a vital pursuit.

Herein, we report the design, synthetic development, and application of an asymmetric nitroaldol procedure for the C–C bond formation to obtain 1,4-diamino-3-hydroxy all *syn* functionalized central core of HIV protease inhibitors ritonavir (**1**)[3] and lopinavir (**2**).[4]

We embarked our study on the synthesis of **6** which was almost free from protection–deprotection and the innovative approach that we adopted adds to the expediency of our method to synthesize valuable β-amino aldehydes in an unprecedented manner.

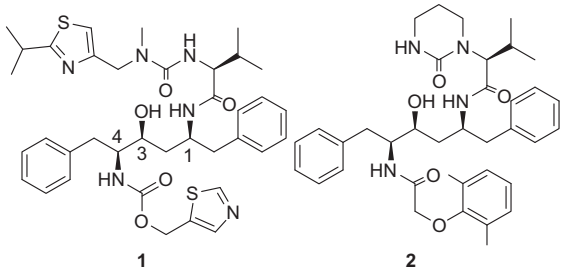

Figure 1. Structure of ritonavir **1** and lopinavir **2.**

Synthesis of **6** starts with the reduction of (*S*)-phenyl alanine **10** with the use of $NaBH_4/H_2SO_4$ system to afford amino alcohol **11** in 74% of yield and 98% of purity.[6] Subsequent chlorination of alcohol **11** led to obtain chlorinated product **12** in excellent yield and purity (79% and 93%) by following the literature procedure[7] that utilizes thionyl chloride for such kind of transformations.

Protection of amino group present in **12** with Boc by using $(Boc)_2O$ and NaOH afforded advanced intermediate **13**.[8] Second order nucleophilic substitution reaction with the use of NaCN on **13** afforded homologated product **14**[9] which was further treated with Raney Ni/Na_2HPO_4/pyridine/AcOH/H_2O[10] to obtain **6** in 61% yield and 90% of purity as shown in Scheme 1. Synthesis of **5** was accomplished by using modified procedure reported in literature.[11]

As outlined in Scheme 2, the 1,4-diamino-2-hydroxy derivative [(2*S*,3*S*,5*S*)-2-amino-3-hydroxy-5-*tert*-butyloxycarbonylamino-1,6-

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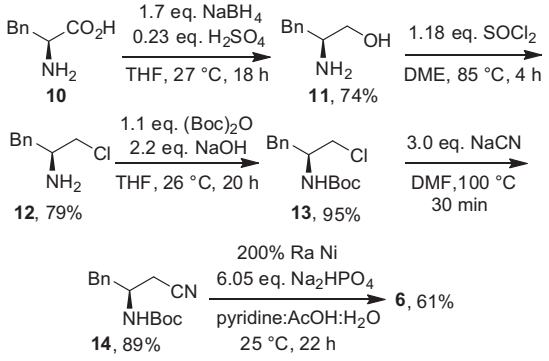
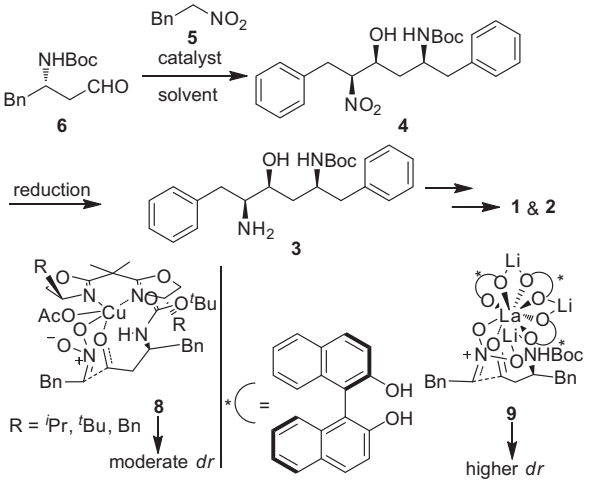


Scheme 1. Synthesis of β-amino aldehyde **6.**



Scheme 2. Diasteroselective nitroaldol approach and plausible *TS* to access **4.**

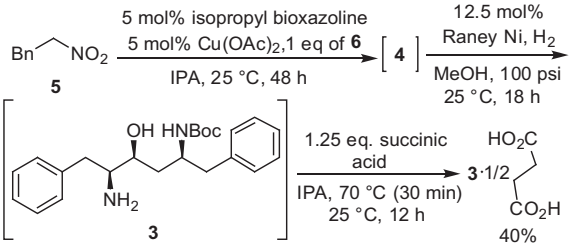
diphenylhexane] **3** may be obtained by employing the nitroaldol strategy. To access the nitroaldol product **4**, catalyst controlled intermolecular nitroalkane **5** (nitronate) additions to the protected β-amino aldehyde **6** were envisioned. In one of the campaigns, C_2 symmetric bisoxazoline ligands **7** were screened. As shown in Scheme 2, the stereochemical outcome is plausibly due to the transition state **8** that afforded the desired 3, 4-*syn* product with *S* configuration at newly generated stereogenic centers.

It can be envisaged that the existing functional group may cause steric hindrance in stereo space with the group(s) present in the catalyst leading to a moderate diastereoselectivity. As shown in Table 1, none of the bisoxazoline variants as a ligand offered excellent diastereoselectivity in the nitroaldol step. The best result in the first screen was obtained with the combination of 5 mol % isopropyl bisoxazoline ligand/Cu(II) catalyst (entry 3) and isopropanol as a solvent affording the desired nitro derivative **4** in promising yield and diastereoselectivity.

Table 1
Asymmetric nitroaldol of aldehyde **6** with **5**

No.	Catalyst	Sol.	°C/h	*dr* (HPLC)	Yield (%) of **4**[a]
1	—	IPA	25/24	No reaction	—
2	$Cu(OAc)_2$	IPA	25/24	No reaction	—
3	^{i}PrBisoxa/$Cu(OAc)_2$	IPA	25/48	62:29:4:5	76
4	^{t}BuBisoxa/$Cu(OAc)_2$	IPA	25/48	52:38:01:9	71
5	BnBisoxa/$Cu(OAc)_2$	IPA	25/48	55:35:5:5	62
6	(R)-BINOL-La-Li	THF	−38/24	80:9:10:1	53

[a] Crude including all the diastereomers based on conversion.



Scheme 3. End game strategy to access **3** hemisuccinate salt.

In another campaign, (*R*)-BINOL-La-Li heterobimetallic catalytic system was employed to obtain enhanced diastereoselectivity. The catalyst displays basic as well as Lewis acid properties. In general, such kind of catalytic system, in the absence of base, catalyzes nitroaldol reaction of aldehydes with nitroalkanes in an excellent enantio/diastereoselective manner.[5]

With our substrates, the *S* configuration at both the newly generated stereogenic centers reflects that the nitronate reacted preferably on the *Si* face of aldehydes in the presence of (*R*)-BINOL-La-Li system that preferentially afforded *syn* selective product **4** which could be attributed to the sterically hindered transition state (**9**) as shown in Scheme 2. As shown in Table 1, we achieved higher dastereomeric ratio (entry 6) than that with bisoxazoline system.

A nitroaldol reaction of aldehyde **6** with phenyl nitroethane **5** was catalyzed in the presence of 5 mol % of (*R*)-BINOL-La-Li at −38 °C, affording nitroaldol product **4** in 53% yield and with diastereoselectivity (80:9:10:1) under stirring for 24 h. Reaction of **6** with **5** was also alternatively performed by using the (*SS*)-isopropyl bisoxazoline and $Cu(OAc)_2$ to obtain **4** in situ in 76% of yield and with *dr* (62:29:4:5). We purified the major all *syn* pair of the nitroaldol adduct **4** and characterized. The *anti* pair, being minor, was not possible to isolate. Conversion of the nitro derivative **4** (in situ), into the desired core **3** (in situ) was achieved by the hydrogenation with Ra Ni under H_2 atmosphere in methanol. After removal of the Ra Ni and distillation of the methanol, the reaction mixture was diluted with isopropanol and subsequently succinic acid was added to obtain hemisuccinate salt of **3** with 40% of yield and 98% of purity as shown in Scheme 3.

In conclusion, we have developed an efficient and operationally simple method for the directed nitroaldol of β-amino acid **6** with nitroderivative **5** to give enatiomerically pure diastereomer, 1,4-diamino-3- hydroxy derivative **3** as a core structure of the HIV protease inhibitors **1** and **2** in good chemical yields and diastereoselectivities.

This approach presents the first example of nitroaldol citing the reaction of an enantiopure protected β-amino aldehyde with a substituted nitroalkane derivative to access 1,4-diamino-3-hydroxy framework. We believe that this strategy will find applications in synthetic organic chemistry.

Acknowledgment

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