Pergamon

Tetrahedron Letters 43 (2002) 8511–8513

TETRAHEDRON LETTERS

A short synthesis of the HIV-protease inhibitor nelfinavir via a diastereoselective addition of ammonia to the α,β-unsaturated sulfoxide derived from (*R*)-glyceraldehyde acetonide

Dawei Ma,* Bin Zou, Wei Zhu and Huadong Xu

State Key Laboratory of Bio-organic and Natural Product Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

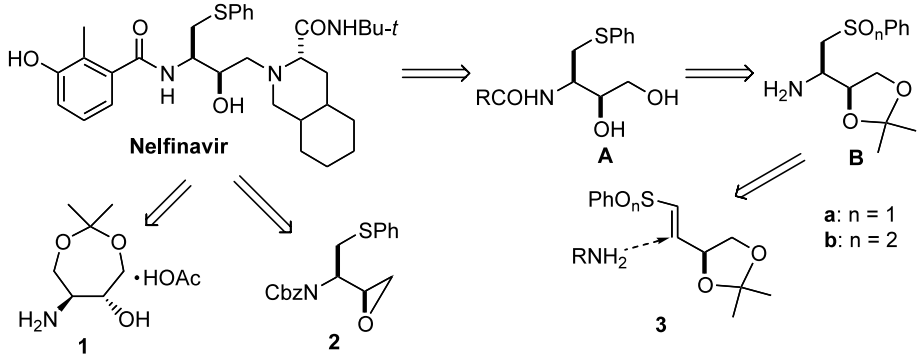
Received 23 July 2002; revised 2 September 2002; accepted 20 September 2002

Abstract—Diastereoselective Michael addition of ammonia to sulfoxide **3a** derived from (*R*)-glyceraldehyde acetonide provides amine **4a**, which is converted into Nelfinavir using $BF_3{\cdot}Et_2O$/NaI reduction and subsequent coupling reactions as key steps.

Nelfinavir mesylate is one of the most potent HIV-protease inhibitors and received FDA approval in March 1997 for treatment of HIV infection.[1] The marketing need and structural complexity have attracted much attention towards its total synthesis.[2–10] To date, several concise protocols have been disclosed.[2–8] Most of these relied on using either (5*R*,6*S*)-2,2-dimethyl-5-hydroxy-1,3-dioxepan-6-ylammonium acetate **1**[5–7] or the epoxide **2**[8] derived from *N*-benzyloxycarbonyl-*S*-phenyl-L-cysteine as an intermediate. The poor diastereoselectivity in obtaining **1** and requirement for many steps to reach **2** prompted us to explore an alternative route.

As shown in Scheme 1, we chose compound **A** as our intermediate, which could be assembled by the reduction of sulfoxide or sulfone **B**. Although there is no report regarding the addition of an amine to olefin **3**, the diastereoselective Michael addition[11] of benzylamine or other amines to α,β-unsaturated esters derived from (*R*)-glyceraldehyde acetonide gave us encouragement that we might be able to prepare **B** from **3** in a diastereoselective manner.

Accordingly, we prepared the olefins **3a** and **3b** by the following methods: (1) trapping the lithium salt generated from methyl phenyl sulfoxide with (*R*)-glyceraldehyde acetonide afforded the corresponding alcohol, which was subjected to mesylation/elimination to provide **3a**;[12] (2) phosphorylation of methyl phenyl sulfone and subsequent Wittig–Horner reaction with



Scheme 1.

* Corresponding author.

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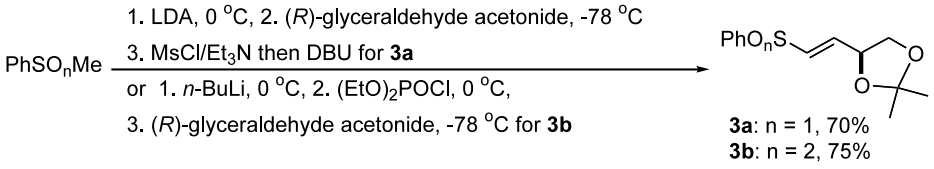
(*R*)-glyceraldehyde acetonide gave **3b** (Scheme 2).[13] The Michael addition of amines to **3a** or **3b** was studied subsequently and the results are summarized in Table 1.

As indicated in Table 1, in the case of benzylamine as a nucleophilic agent, both the sulfoxide **3a** and the sulfone **3b** provided the desired addition products in good yield and diastereoselectivity (entries 1 and 9). However, when ammonia was utilized as a nucleophilic agent, the reaction worked but with lower diastereoselectivity (compare entries 1 and 2). Attempts to overcome this drawback by varying reaction solvents or introducing an additive[11e] failed (entries 3 and 4) or caused slight improvement (entries 5 and 6). In addition, either lowering or raising the reaction temperature resulted in a decrease in diastereoselectivity (compare entries 6–8). The reason for this dramatic change was not clear.

Because both **4b** and **4c** were obtained in a highly diastereoselective manner, we first used them to attempt the further transformations. Thus, Pd/C catalyzed hydrogenation of **4c** provided debenzylated product **6** in 89% yield (Scheme 3). However, the subsequent reduction of the sulfone **6** to the sulfide **7** failed using several reducing reagents such as LAH,[14] DIBAL-H,[15] and $LAH/TiCl_4$.[16] Although later we found a suitable method to reduce the sulfoxide to the corresponding sulfide, the attempt to convert **4b** to **4a** through debenzylation via either hydrogenolysis catalyzed by Pd/C or using Na/NH_3 reductive cleavage also failed. Thus, we had to use **4a**, which was produced by addition of ammonia to **3a**, to progress further (Scheme 4).

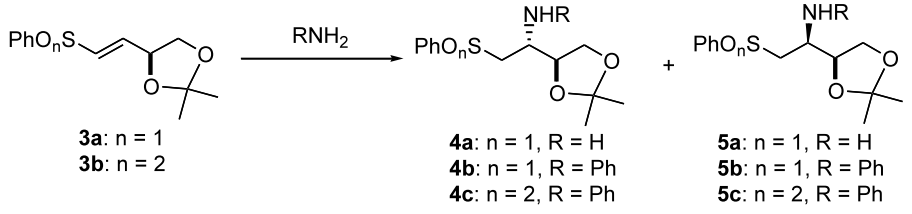
Reduction of the diastereomeric mixture of **4a** and **5a** (Table 1, entries 2 or 6) with $BF_3{\cdot}Et_2O/NaI$ delivered sulfide **8** as a diastereomeric mixture in 71% yield.[17] This conversion was also done by Raney–Nickel catalyzed hydrogenation at room temperature. In this case the yield was slightly higher (80%) than $BF_3{\cdot}Et_2O/NaI$ reduction but the reaction time was much longer (1 week). Coupling **8** with 3-acetoxy-2-methylbenzoic acid mediated by EDCI/HOBt provided separable **9** (72% yield) and its 2-epimer (17% yield). The overall yield from **3a** to **9** was about 40%. Next, hydrolysis of the acetonide moiety of **9** was carried out in 1N HCl/CH_3OH (1:10) at 40°C for 3 h to afford diol **10**. Treatment of this diol with tosyl chloride followed by coupling with the amine **11** furnished Nelfinavir in 59% yield.

In conclusion, we have developed a short and efficient synthesis of Nelfinavir utilizing a novel chiral C4 building block **B** derived from (*R*)-glyceraldehyde acetonide. Further reaction condition optimization to improve the yields and selectivity in some steps is in hand.



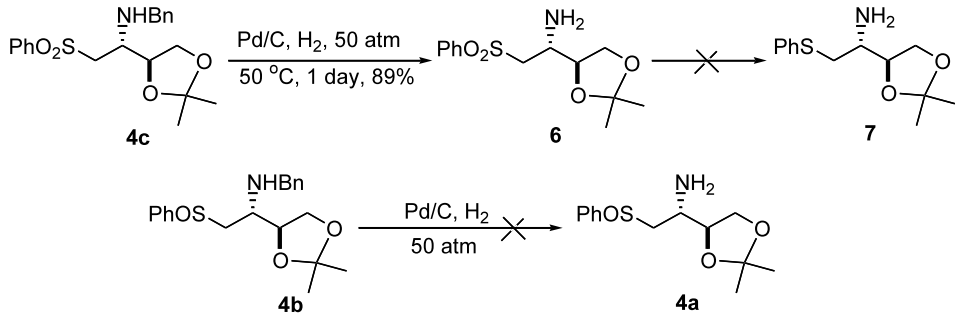
Scheme 2.

Table 1. The Michael addition of amines to olefins **3**[a]

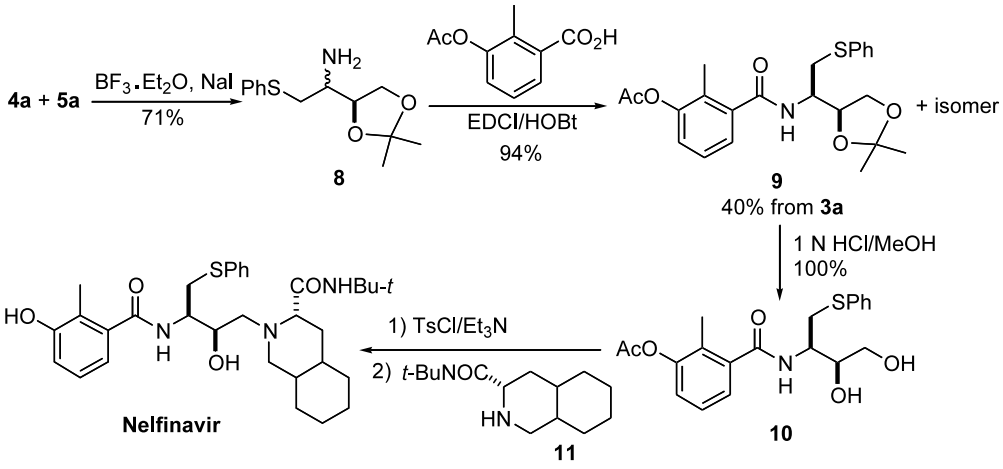


Entry	Substrate	Reaction conditions	Yield (%)[b]	Ratio (**4**/**5**)[c]
1	**3a**	$BnNH_2$/MeOH, reflux, 5 h	85	11/1
2	**3a**	NH_3/MeOH, 60°C, 18 h	81	4/1
3	**3a**	NH_3/EtOH, 60°C, 24 h	68	3.4/1
4	**3a**	NH_3/MeCN, 60°C, 24 h	–[d]	–
5	**3a**	NH_3/MeOH, 10 equiv. LiCl, 60°C, 24 h	78	4.7/1
6	**3a**	NH_3/1/1 MeOH/MeCN, 60°C, 24 h	71	4.7/1
7	**3a**	NH_3/1/1 MeOH/MeCN, 30°C, 4 days	62	3.2/1
8	**3a**	NH_3/1/1 MeOH/MeCN, 100°C, 5 h	80	3/1
9	**3b**	$BnNH_2$/MeOH, reflux, 5 h	78	19/1

[a] Reaction conditions: **3** (0.5 mmol), $BnNH_2$ (10 mmol) or saturated NH_3 in indicated solvent.
[b] Isolated yield.
[c] Determined by HPLC.
[d] No reaction occurred.



Scheme 3.



Scheme 4.

Acknowledgements

The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (grant 20132030), and Qiu Shi Science and Technologies Foundation for their financial support.

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