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# A concise synthesis of the HIV-protease inhibitor nelfinavir via an unusual tetrahydrofuran rearrangement

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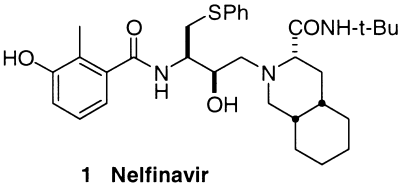
**Abstract**

An efficient synthesis of nelfinavir **1** was developed. The synthesis features an unusual rearrangement of a 3-amidotetrahydrofuran into a functionalized oxazoline. 

The introduction of the HIV protease inhibitors has greatly improved the treatment of HIV infection.[1] Nelfinavir mesylate **1a** received FDA approval in March 1997 and is currently the largest selling protease inhibitor. The combination of large dosing (ca. 2.5 g/day) and structural complexity create a need for an efficient and cost-effective synthesis.




**1 Nelfinavir**
**1a Nelfinavir mesylate salt**

A retrosynthetic analysis of nelfinavir (Scheme 1) shows that nucleophilic ring-opening of an oxazoline **2** using thiophenol can directly afford nelfinavir **1**. Oxazoline **2** can be formed by the coupling of an epoxide precursor **3** and the commercially available perhydroisoquinoline **4**.[2] In the forward sense, this sequence has been carried out by Inaba and co-workers[3] in their synthesis of nelfinavir.

We were interested in alternative syntheses of oxazolines of the type shown in structure **3**. We hypothesized that an intramolecular cyclization of a 3-amido-substituted tetrahydrofuran **5** using an appropriate electrophile could generate oxazolines of the structure **6** (Scheme 2).

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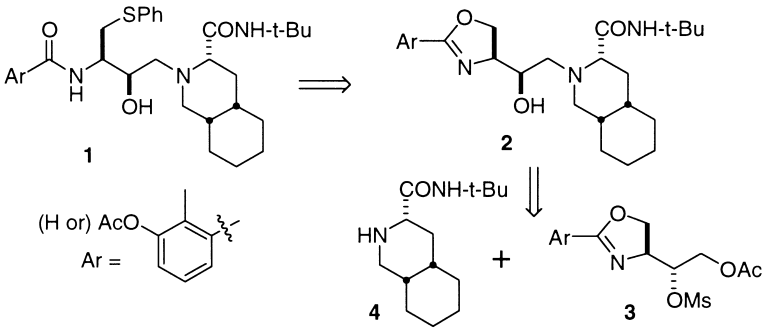
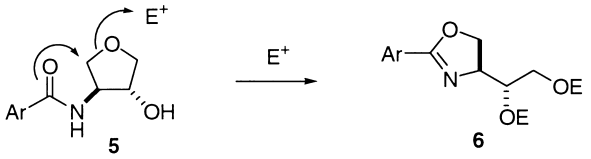


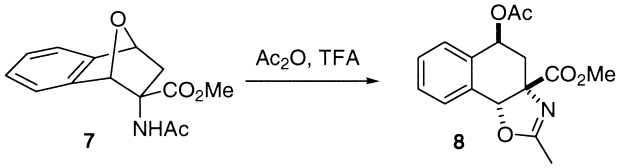

Scheme 1.




Scheme 2.

There is some precedence for cyclizations of this type. McGarvey and co-workers[4] have reported that β-hydroxy-oxazolines can be converted under basic conditions into 3-amido-tetrahydrofurans and that there can be an equilibrium between the two compounds. Iwasaki, Tamaki and co-workers[5] have demonstrated the cyclization of a 2-*endo*-acetamidooxanorbornene **7** to afford the oxazoline **8** (Scheme 3). While this was a promising lead, the ring strain and benzylic nature of the tetrahydrofuran presumably facilitated the cyclization.

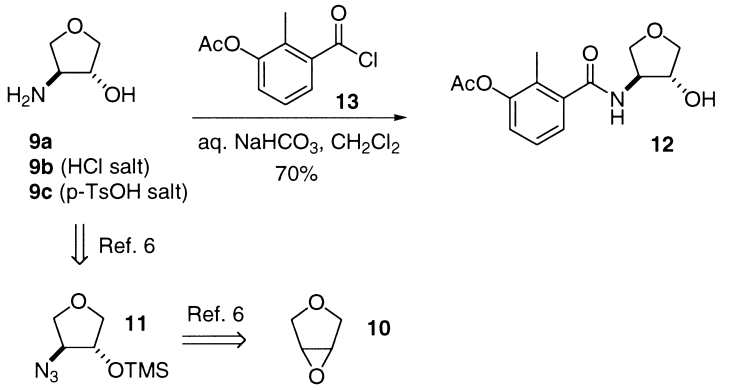
In order to test the cyclization on an appropriate substrate for the synthesis of nelfinavir, the amino alcohol **9a** was required.




Scheme 3.

This compound was readily available from the *meso*-epoxide **10** using the Jacobsen asymmetric desymmetrization via azidotrimethylsilane to afford the azide **11**, followed by reduction and hydrolysis[6] (Scheme 4). We were able to prepare over 500 g of the free amine **9a** using this procedure.[7] The hygroscopic free amine **9a** could also be isolated as the HCl salt **9b** or the *p*-toluenesulfonate salt **9c**.

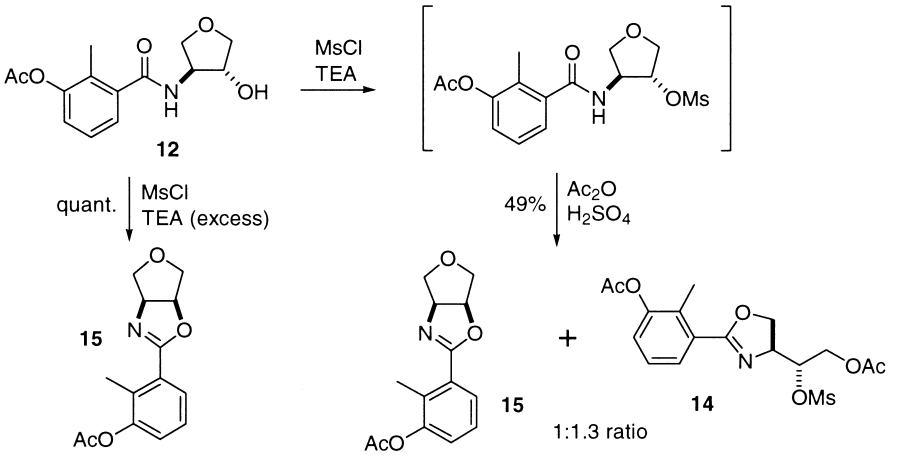
The amino alcohol hydrochloride **9b** was then converted to the amide **12**,[8] corresponding to the amide sidechain of nelfinavir, using the commercially available aryl acid chloride[9] **13** in an average yield of 70%. The moderate yield was due to high water solubility and loss upon workup.




Scheme 4.

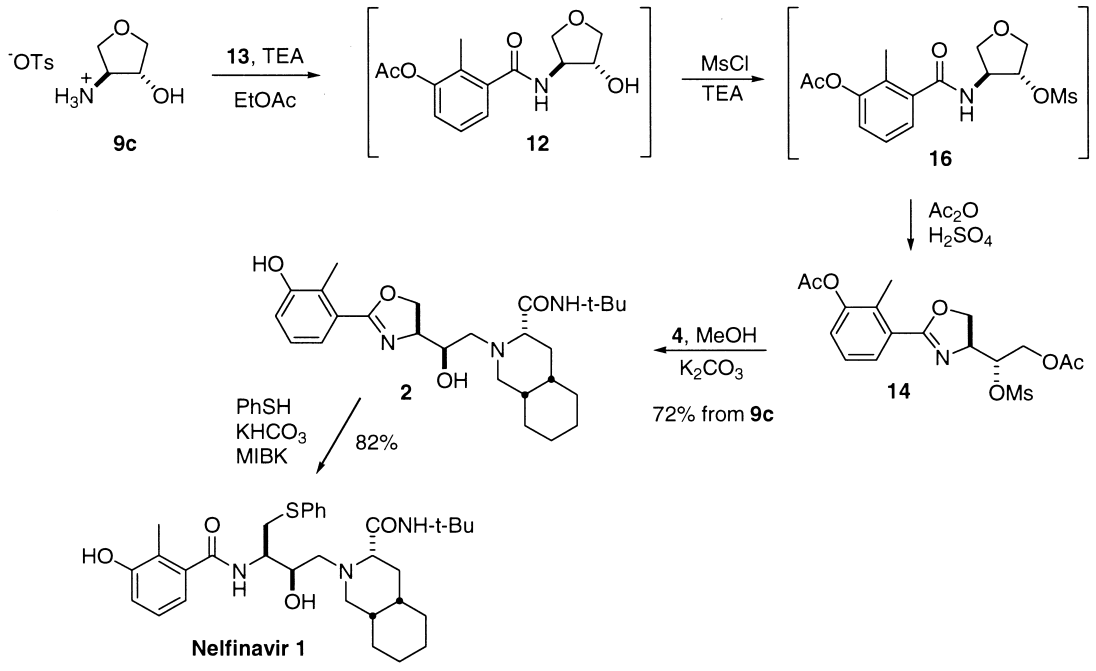
In the cyclization reaction, we found that reaction of amide **12** with 1.1 equiv. of methanesulfonyl chloride and triethylamine (1.2 equiv.) at 0°C followed by acetic anhydride (55 equiv.) and sulfuric acid (2 equiv.) at room temperature afforded a 1.3:1 ratio of the desired oxazoline **14** to the fused oxazoline **15** in a combined 49% yield (Scheme 5).

In order to reduce the amount of the fused oxazoline **15** being formed, we examined the mesylation step. We found that it was advantageous to add the methanesulfonyl chloride first, followed by less than an equivalent amount of triethylamine (with respect to the methanesulfonyl chloride). This reduced the amount of fused oxazoline to less than 5% (by HPLC). The formation of oxazoline **15** was found to be base-induced. Indeed, when the reaction was run using standard mesylation conditions (addition of methanesulfonyl chloride to compound **12** in the presence of 3 equiv. triethylamine), oxazoline **15** was isolated in a quantitative yield.[10] Presumably, the reversed order of addition prevented the build-up of base during the mesylation step. Attempts to isolate the mesylate and subject it independently to the acetic acid/sulfuric acid rearrangement were unsuccessful.




Scheme 5.

We next addressed the moderate yield of amide **12** formation. Since the loss of yield appeared to come from water solubility, the most straightforward approach would be a telescoped process. We found that treatment of the *p*-toluenesulfonate salt **9c** with 2.05 equiv. triethylamine and 1.06 equiv. of 3-acetoxy-2-methylbenzoyl chloride **13** gave an excellent in situ yield (by HPLC) of the amide **12** (Scheme 6). This reaction mixture could then be treated directly with 2.5 equiv. of methanesulfonyl chloride followed by 1.5 equiv. of triethylamine at 0°C. Without workup, this reaction mixture was then treated with 15 equiv. of acetic anhydride and 7.5 equiv. of conc. sulfuric acid, allowing the temperature to rise to 35°C. The ratio and amounts of acetic anhydride and sulfuric acid were found to be necessary for complete oxazoline formation. A neutralization and aqueous workup afforded the oxazoline **14**. Treatment of the crude oxazoline **14** with the perhydroisoquinoline **4** in the presence of aqueous methanol and potassium carbonate gave the adduct **2** (via the epoxide) which crystallized directly from the reaction mixture. A simple methyl-isobutyl ketone reslurry afforded an overall 72% yield of the oxazoline **2** from **9c** in greater than 95% purity.[11]




Scheme 6.

The ring opening of oxazoline **2** by thiophenol occurred in 82% yield as described in Ref. 3, affording nelfinavir free base **1** in high purity.

In conclusion, this work represents a very concise and atom-efficient synthesis of nelfinavir. The total synthesis requires three reactors and two reslurries for purification. There is only one aqueous workup involved.

## References


1. Flexner, C. *N. Engl. J. Med.* **1998**, *338*, 1281–1292.
2. Available from the Aldrich Chemical Company, Inc.
3. Inaba, T.; Birchler, A. G.; Yamada, Y.; Sagawa, S.; Yokota, Y.; Ando, K.; Uchida, I. *J. Org. Chem.* **1998**, *63*, 7582–7583.
4. Wilson, K. J.; Sabat, M.; McGarvey, G. J. *J. Org. Chem.* **1993**, *58*, 6180–6181.
5. Yamazaki, H.; Horikawa, H.; Nishitani, T.; Iwasaki, T.; Nosaka, K.; Tamaki, H. *Chem. Pharm. Bull.* **1992**, *40*, 102–108.
6. Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.*, **1997**, *62*, 4197–4199.
7. We obtained an average yield of 96% over 14 consecutive reactions with a 98% ee on the first run and >99% ee on the subsequent reactions. The azide reduction was performed using a mixture of Pd/C and $PtO_2/H_2$. The catalyst was also recycled through the 14 runs.
8. Spectroscopic data for **12**: mp 141°C. $[\alpha]_D^{25}$ +29.7 (*c* 1.0, MeOH). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.03 (s, 3H), 2.25 (s, 3H), 3.47 (dd, $J$=1.8, 9.3 Hz, 1H), 3.55 (dd, $J$=2.8, 9.0 Hz, 1H), 3.80 (dd, $J$=4.3, 9.3 Hz, 1H), 3.93 (dd, $J$=5.5, 9.0 Hz, 1H), 4.08–4.12 (m, 2H), 5.23 (d, $J$=3.8 Hz, 1H), 7.06–7.23 (m, 3H), 8.50 (d, $J$=6.6 Hz, 1H). $^{13}$C (75 MHz, DMSO-$d_6$) $\delta$ 12.9, 20.9, 58.4, 71.2, 73.8, 75.1, 123.6, 125.2, 126.8, 127.9, 139.3, 149.6, 168.6, 169.3. Anal. calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02; found: C, 60.03; H, 6.10; N, 4.99.
9. Available from the Austin Chemical Company, Inc. 1565 Barclay Blvd. Buffalo Grove, IL 60089, USA.
10. Spectroscopic data for **15**: $[\alpha]_D^{25}$ +18.2 (*c* 1.0, MeOH). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.29 (s, 3H), 2.33 (s, 3H), 3.57 (dd, $J$=3.8, 11.1 Hz, 1H), 3.62 (dd, $J$=5.4, 9.6 Hz, 1H), 3.90 (d, $J$=9.6 Hz, 1H), 4.08 (d, $J$=11.0 Hz, 1H), 4.89 (dd, $J$=5.3, 7.6 Hz, 1H), 5.24 (dd, $J$=3.7, 7.7 Hz, 1H), 7.24 (dd, $J$=1.4, 8.0 Hz, 1H), 7.33 (dd, $J$=8.0, 8.0 Hz, 1H), 7.58 (dd, $J$=1.3, 7.6 Hz, 1H). $^{13}$C (75 Mhz, DMSO-$d_6$) $\delta$ 13.8, 20.9, 72.8, 73.8, 74.4, 82.7, 125.2, 126.9, 127.4, 128.8, 138.8, 150.0, 163.1, 169.4. Anal. calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; found: C, 64.15; H, 5.75; N, 5.32.
11. Representative procedure: The amine salt **9c** (25.0 g, 90.8 mmol) and acid chloride **13** (3-acetoxy-2-methylbenzoyl chloride, 20.4 g, 95.9 mmol) were slurried in ethyl acetate (188 ml) at room temperature. With water bath cooling, triethylamine (25.9 ml, 186 mmol) was added at a rate to keep the temperature below 25°C. The slurry was stirred at room temperature for 1 hour 45 min to give a suspension of **12**. The mixture was then cooled in an ice/acetone bath and methanesulfonyl chloride (17.6 ml, 227 mmol) was added in one portion. Triethylamine (19 ml, 136 mmol) was added dropwise at a rate to keep the internal temperature below 10°C. Acetic anhydride (129 ml) was added in one portion and the cooling bath was removed. Sulfuric acid (98%, 38 ml) was added in three portions at 15-min intervals. The mixture was stirred at room temperature for 17 hours. A suspension of sodium bicarbonate (305 g) in 1 l of water was prepared. This was overlaid with ethyl acetate (250 ml). The reaction mixture from above was added to the sodium bicarbonate slurry dropwise over 2 hours. The layers were separated and the aqueous layer was washed with ethyl acetate (200 ml). The combined organic layers were washed with saturated sodium bicarbonate (200 ml) and brine (200 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated to give oxazoline **14** as an oil. Then **14** was dissolved in methanol (225 ml) and water (225 ml) was added. Potassium carbonate (37.6 g, 272 mmol) and perhydroisoquinoline **4** (20.5 g, 86.1 mmol) were added sequentially. The mixture was heated to 50°C for 5 hours. Water (225 ml) was added to the slurry, which was allowed to cool to room temperature. The solid **2** was filtered, washed with water and dried in a vacuum oven at 42°C. The crude yield of **2** was 45 g. The crude **2** was slurried at room temperature in methyl-*iso*-butyl ketone (400 ml) for 30 min and filtered and washed with MIBK (100 ml). The purified **2** was dried in a vacuum oven at 42°C to constant weight. The yield was 29.9 g, 72%. Spectral data for compound **2** was consistent with that reported in Ref. 3.