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A synthesis of the HIV-protease inhibitor nelfinavir from D-tartaric acid

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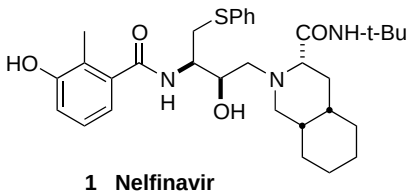
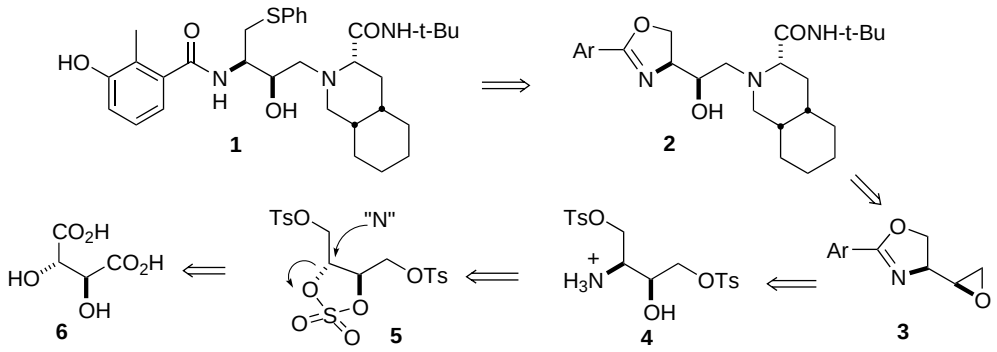
Abstract—This letter describes a new synthesis of the HIV-protease inhibitor nelfinavir. The synthesis features a selective opening of a D-tartaric acid-derived cyclic sulfate with nitrogen nucleophiles. © 2001 Published by Elsevier Science Ltd.

The HIV-protease inhibitors, as a class, possess a fairly complex structure and are a synthetic challenge to produce economically on the metric ton scale. Nelfinavir **1** contains five chiral centers with a core four-carbon backbone in which each carbon is attached to a heteroatom.[1]



1 Nelfinavir

Our interest in four-carbon synthons led us to examine the chemistry of D-tartaric acid.[2] While the D-isomer is the 'unnatural' tartaric acid, it is available on commercial scale.[3] One of the keys to using D-tartaric acid for the synthesis of nelfinavir was the introduction of a nitrogen at an appropriate time in the synthesis. Scheme 1 shows a retrosynthetic strategy for the synthesis of nelfinavir from D-tartaric acid. The thiophenol moiety could be introduced late in the sequence by the ring-opening of an oxazoline **2**, while the perhydroisoquinoline can be introduced by epoxide opening of an intermediate such as **3**. Inaba and co-workers have demonstrated these steps in a related synthesis of nelfinavir.[4]



Scheme 1.

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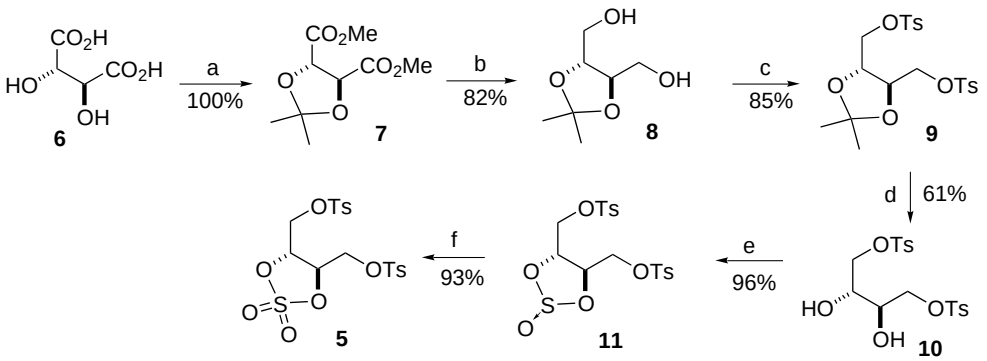
The epoxy-oxazoline **3** could be synthesized from aminoalcohol intermediate **4** which contains the oxazoline nitrogen and appropriate leaving groups. In the key reaction, opening of cyclic sulfate **5** with a nitrogen nucleophile, in the presence of two primary tosylates, could directly give **4**. We envisaged that the increased electrophilic reactivity of a cyclic sulfate versus an alkyl sulfonate would allow exclusive substitution at the cyclic sulfate carbon on an ambident electrophile. The chiral centers in cyclic sulfate **5** could be derived from D-tartaric acid **6**.

The synthesis of the cyclic sulfate **5** from D-tartaric acid proved to be straightforward and is shown in Scheme 2.[5]

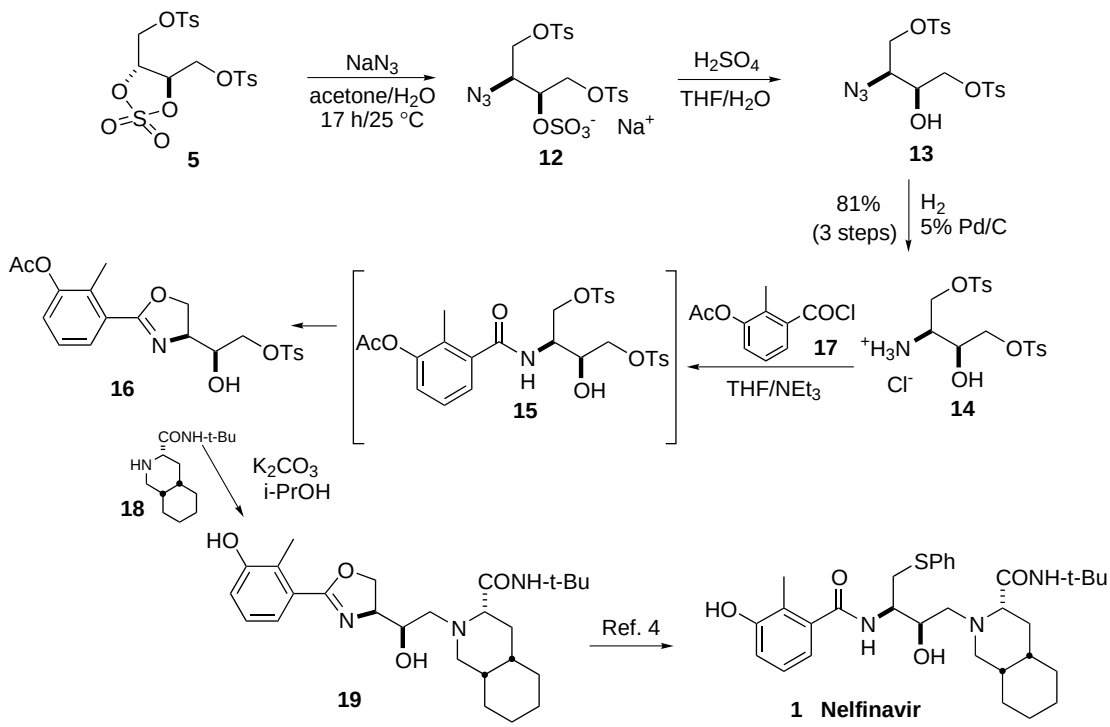
D-Tartaric acid was converted to the acetonide-diester **7**[6] followed by sodium borohydride reduction[7] to the water-soluble diol **8**. Tosylation gave the intermediate **9** and subsequent hydrolysis of the crude acetonide afforded diol **10**. A two-step synthesis of the cyclic sulfate **5** involved sulfite formation to give **11** and a separate ruthenium(III) chloride-catalyzed oxidation to the cyclic sulfate.[8]

The successful synthesis of the cyclic sulfate **5** allowed us to begin examination of its ambident electrophilicity with respect to the addition of nitrogen nucleophiles. Reaction of sodium azide with the cyclic sulfate **5** in aqueous acetone gave clean conversion (HPLC) to the ring-opened azido-sulfate salt **12** (Scheme 3).[9]

The hydrolysis of **12** generally required stirring in aqueous acid. Aware of the hazard of generating hydrazoic acid from unreacted azide ion, the bulk of the solvents were evaporated from **12** and the resulting



Scheme 2. *Reagents and conditions*: (a) dimethoxypropane, TsOH, MeOH cyclohexane, 52–54°C azeotrope; (b) $NaBH_4$, EtOH, 20°C, 2.5 h; (c) *p*-TsCl, NEt_3, MTBE 30°C, 17 h; (d) 95% EtOH, 1N HCl, reflux 3 h; (e) $SOCl_2$, CH_2Cl_2, rt, 18 h; (f) cat. $RuCl_3$, $NaIO_4$, CH_3CN/H_2O.



Scheme 3.

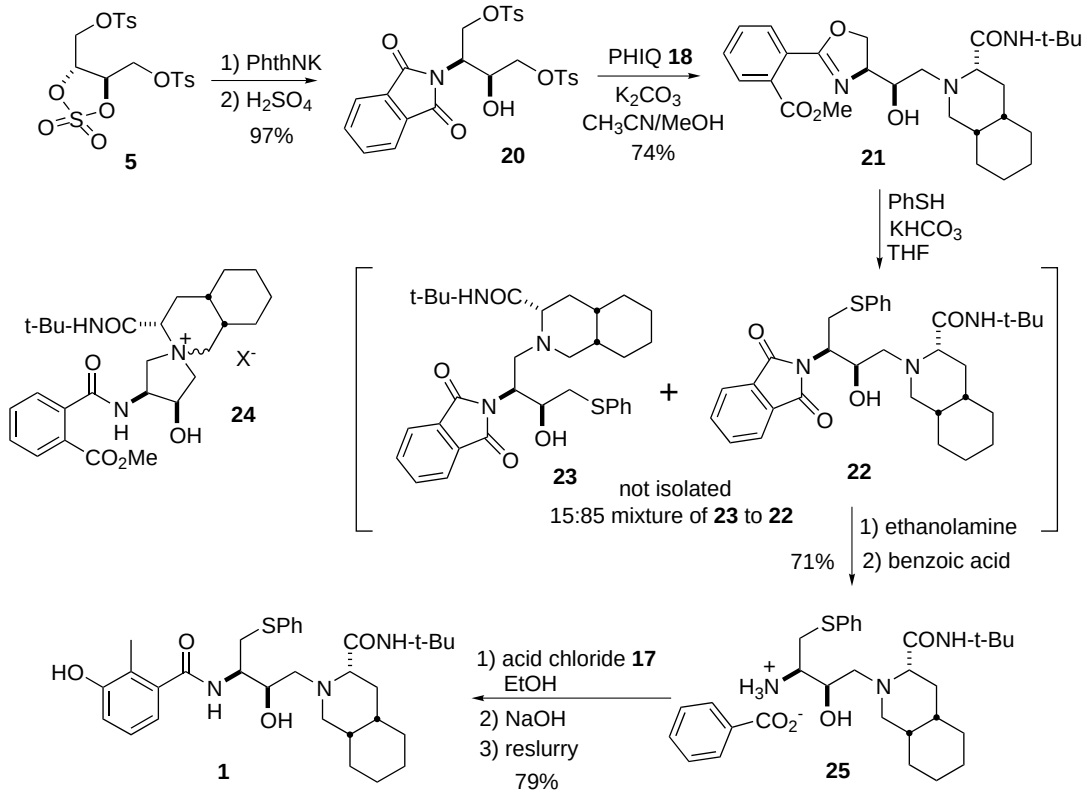
white solids were filtered and washed with water. The wet-cake was then dissolved in THF and a catalytic amount of sulfuric acid was added. No additional water was added and, in fact, our experience with the hydrolysis of this type of sulfate salt showed that excess water is a detriment.[10] In order to achieve complete hydrolysis, the reaction mixture had to be filtered through sodium sulfate in order to remove some of the excess water. Azidoalcohol **13** was fully characterized[11] and was shown to be the product of exclusive opening at the cyclic sulfate carbon center. To date, we have not observed the product resulting from attack of a nucleophile at the primary carbon-bearing tosylate.

Generally, the azidoalcohol **13** reaction mixture was directly diluted with methanol and hydrogenated using 5% Pd on carbon in the presence of 6N HCl. The amine hydrochloride salt **14** was isolated as an oil in 81% yield from the cyclic sulfate **5**. The amine salt **14** was then converted via the amide **15** to the oxazoline **16** by acylation with the commercially available[12] acid chloride **17**, corresponding to the amide sidechain of nelfinavir. The amide **15** was not isolated and appeared to rapidly cyclize to the oxazoline **16** under the reaction conditions. Cyclization to the oxazoline gave the added benefit of differentiating the two terminal carbons of **15**. Epoxide formation and opening with perhydroisoquinoline (PHIQ) **18**[13] was accomplished by heating the crude **16** with potassium carbonate and the amine **18** in one-pot to afford the oxazoline **19** in 51% overall yield from the amine salt **14**. The synthesis of nelfinavir **1** was completed by opening of oxazoline **19** with thiophenol in 82% yield.[4]

The inherent problems associated with the use of azide led us to look for alternative amine nucleophiles for the opening of cyclic sulfate **5**. Unfortunately, common nitrogen nucleophiles such as benzylamine, dibenzylamine, *p*-toluenesulfonamide, formamide or sodium diformylamide gave no reaction or decomposition using more aggressive conditions. We did find that potassium phthalimide resulted in very clean addition to the cyclic sulfate (Scheme 4). This sequence emerged as an efficient synthesis of nelfinavir.

Addition of potassium phthalimide to cyclic sulfate **5** followed by in situ hydrolysis of the sulfate gave the phthalimido alcohol **20** in 97% yield as an isolated solid. Epoxide formation and opening with the perhydroisoquinoline **18** was now accompanied by opening of the phthalimide by methoxide,[14] and subsequent cyclization of the amide onto the primary tosylate, which gave the oxazoline **21** in 74% isolated yield.

Opening of the oxazoline with thiophenol (4 equiv.) in the presence of potassium bicarbonate at THF reflux gave an 85:15 mixture of sulfides **22** and **23** which were not generally isolated. The formation of the undesired isomer **23** appears to arise from formation of a quaternary spirocyclic ammonium salt such as **24**.[15] Thiophenol attack could then occur at two sites of the five-membered ring. We have not observed products from thiophenol opening of the six-membered ring. Interestingly, when oxazoline **21** was allowed to react with 1 equiv. of trifluoroacetic acid in acetonitrile, quaternary salt **24** (X = trifluoroacetate) was obtained



Scheme 4.

as the exclusive product as a mixture of diastereomers. One of these diastereomers has been completely characterized by ^{1}H NMR.[16] When the TFA salt of **24** was subjected to the thiophenol reaction conditions, a 27:73 ratio of **22** to **23** was obtained, showing that quaternization is a pathway that leads to the undesired isomer. Again, no products arising from nucleophilic attack on the six-membered ring were observed.

The reaction mixture containing **22** and **23** was treated with ethanolamine at reflux to cleave the phthalimide. After an aqueous workup, an MTBE solution of the free amine was treated with benzoic acid and the benzoate salt **25** crystallized from the mixture upon dilution with hexanes in 71% yield. This salt formation gave us a very good purification opportunity for the nelfinavir synthesis, being the penultimate intermediate. The product formed from ethanolamine cleavage of the undesired isomer **23** was completely removed by this crystallization. Conversion of **25** to the freebase, acylation with the acid chloride **17**, and hydrolysis of the phenolic acetate afforded nefinavir **1** in 79% yield after two acetone/water reslurries. The nelfinavir passed all purity specifications. The above sequence has been demonstrated on a multi-kilogram scale.

In conclusion, we have developed an effective synthesis of nelfinavir utilizing a key nucleophilic opening of a cyclic sulfate. The cyclic sulfate is readily derived from D-tartaric acid through a series of simple transformations in high yield. We have also replaced the use of hazardous sodium azide through the use of potassium phthalimide. Additionally, the potassium phthalimide nucleophile served a dual role as protecting group and oxazoline precursor.

Acknowledgements

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8. All new compounds exhibited satisfactory spectral (300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, IR), and high-resolution mass spectral characteristics. Spectroscopic data for **5**: mp 103°C; $[\alpha]_D$ 54.7 ($c=1.0$, MeOH); IR (KBr) ν_{max} 1397, 1211, 1179, 814 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.80 (4H, d, $J=8.4$ Hz), 7.51 (4H, d, $J=8.4$ Hz), 5.24 (2H, m), 4.48 (4H, m), 2.43 (6H, s); ^{13}C NMR ($CDCl_3$) δ 146.5, 131.8, 130.7, 128.54, 78.8, 65.7, 22.2; HRMS calcd for $C_{18}H_{21}O_{10}S_3$ 493.0297, found 493.0294.
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11. Spectroscopic data for **13**: mp 82°C; $[\alpha]_D$ 24.2 ($c=1.0$, MeOH); IR (KBr) ν_{max} 3580, 2092, 1360 cm^{-1}; ^{1}H NMR (DMSO-d_6) 7.79 (2H, d, $J=8.1$ Hz), 7.76 (2H, d, $J=8.1$ Hz), 7.50 (2H, d, $J=8.1$ Hz), 7.48 (2H, d, $J=8.1$ Hz), 5.75 (1H, br s), 4.28 (1H, dd, $J=2.8$, 10.7 Hz), 4.08 (1H, dd, $J=7.2$, 10.5 Hz), 4.02 (1H, dd, $J=3.3$, 10.5 Hz), 3.94 (1H, dd, $J=5.4$, 10.5 Hz), 3.76 (1H, ddd, $J=3.0$, 7.2, 7.5 Hz), 3.63 (1H, ddd, $J=3.0$, 5.1, 7.8 Hz); ^{13}C NMR (DMSO-d_6) δ 145.7, 145.4, 132.3, 132.1, 130.6, 130.5, 128.0, 71.7, 69.8, 67.4, 60.8, 21.5; HRMS calcd for $C_{18}H_{22}N_3O_7S_2$ 456.0899, found 456.0893.
12. Available from Austin Chemical Company, Inc. 1565 Barclay Blvd. Buffalo Grove, IL 60089, USA.
13. Available from the Aldrich Chemical Company, Inc.
14. Weigel and Astleford have used the pyrrolidine adduct to attenuate the reactivity of the phthalimide group. Astleford, B.; Weigel, L. O. *Tetrahedron Lett.* **1991**, *32*, 3301–3304.
15. Inaba and co-workers (Ref. 4) have also proposed a spirocyclic ammonium intermediate as the source of a related regioisomer.
16. NMR experiments (^{1}H NMR, DQF-COSY, HMQC and HMBC) were acquired at 500 MHz on the mixture of diastereomers in DMSO-d_6 at 30°C. These data clearly established the presence of the quaternary spirocycle for a single diastereomer in the mixture. The DQF COSY defined the ^{1}H spin system involving the benzamide proton NH_a and protons attached to carbons C1–C4, along with two additional spin systems assigned to protons at C5–C6 and C12–C13. The HMQC and HMBC experiments provided unambiguous proton and carbon resonance assignments for NH_a, C1–C7, C12–C13, C19, and the *t*-butylamide nuclei. Over 20 long range ^{1}H–^{13}C correlations involving these nuclei were observed, including key correlations from the protons at C1 to carbons

C4, C5, and C13 (denoted by arrows), which together defined the spirocyclic quaternary ammonium salt. Resonances for nuclei definitively assigned to a single diastereomer are summarized as follows: (^{1}H/^{13}C) δ 3.53, 4.06/66.0 (C1); 4.74/50.0 (C2); 4.36/68.0, (C3); 3.84 2H/68.7 (C4); 4.19/68.3 (C5); 1.90, 2.57/31.4 (C6); 1.76/30.1 (C7); 2.19/28.8 (C12); 3.35, 4.58/59.8 (C13); 167.6 (C14); 8.25 NH_b; 50.7 (C15); 1.31/27.8 (C16–C18); 8.53 NH_a; 168.0 (C19).