A Practical Synthesis of Nelfinavir, an HIV-Protease Inhibitor, Using a Novel Chiral C4 Building Block: (5*R*,6*S*)-2,2-Dimethyl-5-hydroxy-1,3-dioxepan-6-ylammonium Acetate

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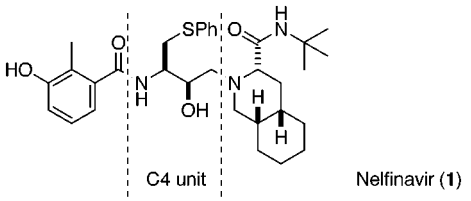
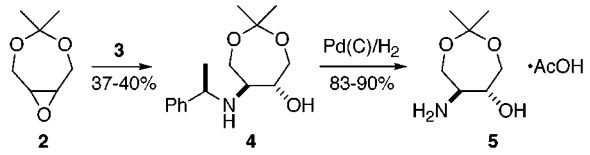
Nelfinavir mesylate,[1] one of the most potent HIV-protease inhibitors,[2] comprises three retrosynthetic components: a chiral C4 unit, a perhydroisoquinoline derivative unit, and a benzoic acid derivative unit. The preparation of the perhydroisoquinoline derivative has been previously addressed in the literature,[3] and the substituted benzoic acid derivative can be prepared using well-known chemistry.[4] However, the design of a chiral C4 unit that could be efficiently constructed and coupled to the two aforementioned units has proven to be nontrivial. This C4 unit was previously prepared from L-serine via multiple steps, including C1 elongation and diastereomeric reduction, which required low-temperature reaction conditions and expensive reagents.[5] Described herein is a practical synthesis of nelfinavir free base (**1**), in which (5*R*,6*S*)-2,2-dimethyl-5-hydroxy-1,3-dioxepan-6-ylammonium acetate (**5**) is employed as a new chiral C4 building block.



As the starting material for the C4 unit we focused on epoxide **2**.[6] Despite its lack of chirality, **2** provided several advantages, including the desired four-carbon arrangement with the correct oxidation state for all four carbons. Additionally, as a meso compound, **2** avoided the necessity for a regioselective aminolysis. Upon refluxing in 2-propanol with 1 equiv of (*R*)-α-methylbenzylamine (**3**), **2** underwent S_N2 ring opening[7] to provide a diastereomeric mixture of *trans*-amino alcohol. The more polar isomer (**4**) was easily and consistently isolated from the one-pot reaction by crystallization in 37−40% yield with >99% de.[8] Reduction of the methylbenzyl group of **4** in the presence of 1 equiv of acetic acid gave enantiomerically pure **5**.[9]



The employment of **5** as a chiral C4 unit in the synthesis of **1** required (a) differentiation of the two acetonide protected primary hydroxyl groups and (b) inversion of the asymmetric center possessing the secondary hydroxyl group. Differentiation of the primary hydroxyl groups was anticipated to be accomplished by the coupling of **5** with the benzoic acid moiety with subsequent intramolecular oxazoline ring formation involving the adjacent primary hydroxy group. Inversion of the secondary hydroxyl group was expected to be achieved by mesylation followed by intramolecular S_N2 displacement by the α-hydroxyl group. This strategy was successfully executed using simple and reliable synthetic methodologies that yielded **1** with high and reproducible yields.

The coupling of **5** with acid chloride **6** gave amide alcohol **7**, which was subsequently treated with methanesulfonyl chloride to afford mesylate **8** (Scheme 1). When **8** was treated with $BF_3{\cdot}Et_2O$ followed by quenching with acetic anhydride, **10** was obtained in 65−71% yield from **5**. Alternatively, the unstable alcohol **9** was isolated by quenching the $BF_3{\cdot}Et_2O$ reaction with water. Oxazoline ring formation and concomitant deprotection of the acetonide group achieved complete differentiation of the two primary hydroxyl groups generated by the deprotection. A plausible mechanism for the oxazoline formation is the concerted nucleophilic attack of the amide oxygen with the acetone of the acetonide protecting group serving as a leaving group. Quenching the reaction with acetic anhydride[10] or water provided **10** or **9**, respectively. Treatment of **10** with K_2CO_3 in the presence of perhydroisoquinoline **12**[3] in aqueous methanol gave **13** via the unstable epoxide **11**. Under these reaction conditions, saponification of the two acetate groups of **10**, epoxide formation, and nucleophilic attack at the terminal carbon of the epoxide by **12** took place successively with inversion of the asymmetric center bearing the methanesulfonyloxy group. Compound **13** crystallized from the reaction mixture and was isolated in 62−65% yield from **5**. All of the above reactions proceeded cleanly, and no isolation or purification was required for any of the intermediates between **5** and **13**.

The final transformation in the synthesis of **1** was the ring opening of the oxazoline ring with PhSH.[11] This reaction

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(1) Kaldor, S. W.; Kalish, V. J.: Davies, J. F., II; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.

(2) For a review of recent HIV-protease inhibitors, see: Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.

(3) (a) Houpis, I. N.; Molina, A.; Reamer, R. A.; Lynch, J. E.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1993**, *34*, 2593. (b) Gohring, W.; Gokhale, S.; Hilpert, H.; Roessler, F.; Schlageter, M.; Vogt, P. *Chimia* **1996**, *50*, 532.

(4) See the Experimental Section in the Supporting Information.

(5) (a) Marzoni, G.; Kaldor, S. W.; Trippe, A. J.; Shamblin, B. M.; Fritz, J. E. *Synth. Commun.* **1995**, *25*, 2475. (b) Rieger, D. L. *J. Org. Chem.* **1997**, *62*, 8546.

(6) Elliott, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469. **2** was prepared by the oxidation of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin with H_2O_2/MeCN in place of *m*-CPBA, which was used in the reported method. The detailed procedure is shown in the Supporting Information.

(7) (a) Bair, K. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem.* **1990**, *33*, 2385. (b) Aube, J.; Wolfe, M. S.; Yantiss, R. K.; Cook, S. M., Takusagawa, F. *Synth. Commun.* **1992**, *22*, 3003.

(8) The stereochemistry of **4** (>99% de; mp 108−109 °C; $[\alpha]^{25}_D$ +96.2 (c 1.00, MeOH)) was determined by X-ray crystallographic analysis (see the Supporting Information). The atomic coordinates have been deposited with CCDC (Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK).

(9) Experimental data: >99% ee (HPLC); mp 133−134 °C; $[\alpha]^{25}_D$ +29.6 (*c* 1.05, MeOH). See the Supporting Information.

(10) Nagao, Y.; Fujita, E.; Kohno, T.; Yagi, M. *Chem. Pharm. Bull.* **1981**, *29*, 3202.

(11) Padgette, S. R.; Herman, H. H.; Han, J. H.; Pollock, S. H.; May, S. W. *J. Med. Chem.* **1984**, *27*, 1354.

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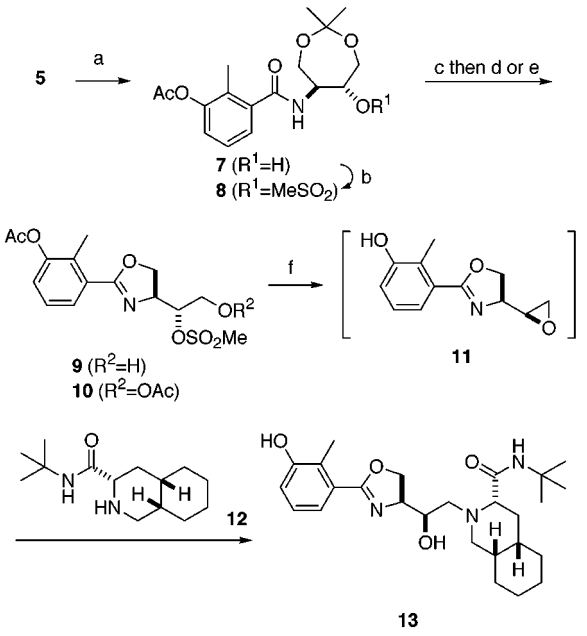
Scheme 1[a]



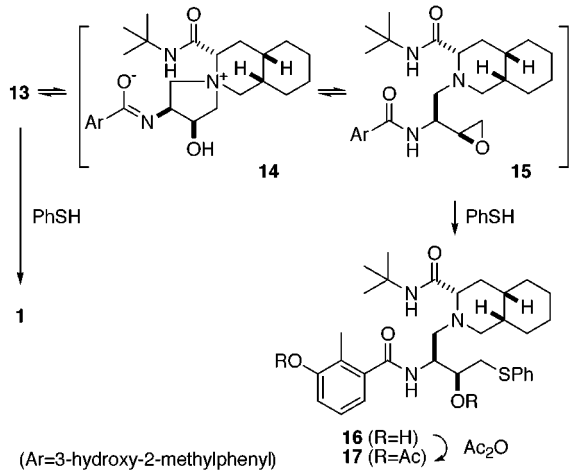
[a] Reaction conditions: (a) 3-acetoxy-2-methylbenzoyl chloride (**6**), $NaHCO_3$, CH_2Cl_2, H_2O; (b) $MeSO_2Cl$, NEt_3, CH_2Cl_2; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2; (d) H_2O (for **9**); (e) Ac_2O (for **10**); (f) K_2CO_3, MeOH, H_2O, **12**.

Table 1. Regioselectivity of the Reaction of 13 with PhSH[a]

entry	base (equiv)	solvent	*T* (°C)	time (h)	ratio[b] (**1**:**16**)
1	none	$HOCH_2CH_2OH$	120	20	18:82
2	none	DMF	85	16	71:29
3	NEt_3 (4.0)	DMF	80	10	84:16
4	$KHCO_3$ (2.0)	MIBK[c]	115	4	92:8

[a] All reactions were performed using 4.0 equiv of PhSH, except that 2.0 equiv of PhSH was employed in entry 4. [b] Regioisomer ratio, by HPLC of the reaction mixture at completion. [c] Methyl isobutyl ketone.

was accompanied by a byproduct, the undesired regioisomer **16**.[12] The regioselectivity (**1**:**16**) of the process was effected by the selection of solvents and bases, as shown in Table 1. When the reaction was conducted in ethylene glycol (entry 1), **16** was the predominate product. Use of a less polar solvent (DMF) reversed the selectivity, and the desired compound **1** became the predominant product (entry 2). The selectivity was further improved when the reaction was carried out in the presence of an organic or inorganic base in the less polar solvents (entries 3 and 4). The reaction conditions outlined in entry 4 provided pure isolated **1** in 81−84% yield from **13**. Desired **1** could be generated through the direct ring opening of the oxazoline moiety of **13** by the nucleophilic attack of PhSH. The generation of **16** could be explained by the formation of epoxide **15** through a transient cyclic quaternary amine **14**, although it was unable to observe the formation of **15** under the reaction conditions in the presence or absence of PhSH.[13] It has been speculated that **14** arises from **13** via an intramolecular ring opening of the oxazoline by nucleophilic attack of the perhydroisoquinoline nitrogen atom. The choice of solvent and base may effect the stabilization of intermediate **14** and the nucleophilicity of PhSH, thus influencing the ultimate regioselectivity of the reaction.



In summary, a concise synthesis of the potent anti-HIV drug nelfinavir (**1**) was accomplished using a novel chiral C4 unit (**5**). A key component in this synthetic strategy was the utilization of an oxazoline intermediate. First, the two protected primary hydroxyl groups of **5** were differentiated using a unique $BF_3{\cdot}Et_2O$-mediated intramolecular oxazoline ring formation (**8** to **10**). This oxazoline ring then served as an electrophilic center for the introduction of the phenylthio group (**13** to **1**). The aromatic substituent group on the oxazoline remained in the structure of the final product **1**. This practical synthesis provides **1** from an easily accessible starting material (**5**) in greater than 50% overall yield. It is expected that **5** should also be useful in the production of other chiral synthetic targets of biological interest.

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Supporting Information Available: Experimental procedures, analytical and spectral data for all new compounds, and crystal structure data for **4** and **17** (31 pages).

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(12) The structure of **16** was confirmed by X-ray crystallographic analysis of diacetate **17** derived from **16** (see the Supporting Information). The atomic coordinates have been deposited with CCDC.

(13) The nucleophilic attack of PhSH on **14** was ruled out as a mechanism for the formation of **1** and **16** because it seemed unlikely that PhSH selectively cleaved two of four $C-N^+$ bonds in **14** to form **1** and **16**. No byproduct other than **16** was detected in the reactions listed in Table 1 (HPLC).