A Concise Formal Synthesis of the Potent HIV Protease Inhibitor Nelfinavir Mesylate

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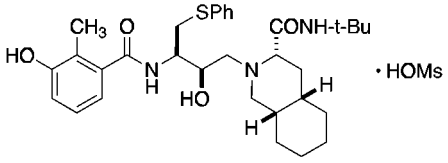
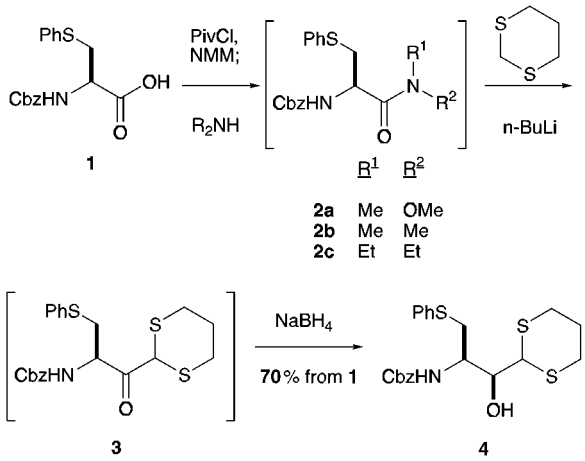
Nelfinavir mesylate (AG1343) is a potent, orally active inhibitor of HIV protease and has recently been approved by the US FDA as a treatment for HIV infection.[1] We required an efficient, large-scale process for production of the large quantities of AG1343 needed for clinical development and for eventual market launch. Here, we report some of our studies in this area, which have led to a concise formal synthesis of AG1343.



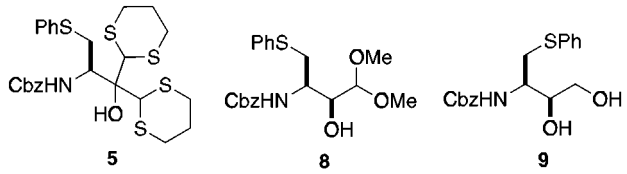
AG1343

As the starting material for our synthetic efforts, we chose *N*-Cbz-*S*-phenyl-L-cysteine (**1**). This compound was readily available on large scale from L-serine.[2] Derivatization of **1** as its Weinreb amide **2a** proceeded without racemization *via* the pivaloyl mixed anhydride.[3] Addition of 2-lithio-1,3-dithiane (generated from 1,3-dithiane and *n*-BuLi at 0 °C) gave ketone **3**, which was reduced *in situ* with sodium borohydride at 0 °C to provide the desired dithianyl alcohol **4** in 64% yield from **2a**. The diastereoselectivity in the reduction was 82:18 in favor of **4**.[4] Use of DIBAL in the reduction of **3** gave reversed stereoselectivity (1:2), as would be predicted by a Felkin-type addition to **3**. This indicates either that the hydride in the $NaBH_4$ reduction is delivered through coordination of the reductant with the carbamate moiety or that the reduction proceeds through an anti-Felkin-type transition state.

Further investigation of the conversion of *N*-Cbz-*S*-phenyl-L-cysteine to dithianyl alcohol **4** revealed that the relatively inexpensive dimethyl amide derivative **2b** functioned equally well in the addition of 2-lithio-1,3-dithiane as compared to the Weinreb amide **2a**. Thus, addition of 3 equiv of 2-lithio-1,3-dithiane to crude **2b** (88% ee) formed **3**. The reaction was quenched with an organic acid (HOAc) prior to aqueous workup to prevent racemization of the chiral center.[5] Reduction of the crude



ketone **3** with $NaBH_4$ (0.5 molar equiv, MeOH/THF (2/1), 4 °C) gave **4** after aqueous workup and crystallization from EtOAc/hexanes (1/3, 8 mL/g crude **3**). The overall yield of **4** from **1** was 70% on a 40-g scale. The ee of the product (**4**) was 83%.[6] The diastereomeric ratio, 82/18 in the crude product, was 98/2 in isolated **4**. Overaddition of the organolithium species was not a problem, since none of alcohol **5** was isolated from the reaction mixture. Attempted addition of 2-lithio-1,3-dithiane to the even less expensive diethyl amide derivative **2c** did give the desired ketone **3**, but the reaction was not as clean, resulting in **3** which was not as pure as that derived from **2b**. The reason for the differing reactivity of **2b** and **2c** may at least in part be due to the increased steric bulk surrounding the carbonyl group in **2c**.



Completion of the synthesis of AG1343 required removal of the dithianyl group in **4** in the presence of the phenylthio group to give α-hydroxy aldehyde **6**. Reductive amination of this aldehyde with perhydroisoquinoline **7**[7] would give AG1357 which has previously been converted to AG1343.[8] Several methods were studied for removal of the dithianyl moiety (MeI, H_2O; $HgCl_2$; CAN; MeOTs, H_2O; $NaIO_4$, H_2O; OHCCOOH, HOAc, HCl; CuO, $CuCl_2$; DDQ).[9] These methods were either too vigorous (i.e., $HgCl_2$; CAN; CuO, $CuCl_2$) or too sluggish (i.e., MeI, H_2O; MeOTs, H_2O) to afford high yields of **6**. The method that finally gave reasonable yields (ca. 80%) of the desired aldehyde was $Hg(ClO_4)_2 \cdot 3H_2O$ in a mixture of IPA, $CHCl_3$, and H_2O (3/6/1) at ambient temperature.[9h,10] This

(1) Appelt, K.; Bacquet, R. J.; Bartlett, C.; Booth, C. L. J.; Freer, S. T.; Fuhry, M. M.; Gehring, M. R.; Herrmann, S. M.; Howland, E. F.; Janson, C. A.; Jones, T. R.; Kan, C. C.; Kathardekar, V.; Lewis, K. K.; Marzoni, G. P.; Mathews, D. A.; Mohr, C.; Moomaw, E. W.; Oatley, S. J.; Ogden, R. C.; Reddy, M. R.; Reich, S. H.; Schoettlin, W. S.; Smith, W. W.; Varney, M. D.; Villafranca, J. E.; Ward, R. W.; Webber, S.; Webber, S. E.; Welsh, K. M.; White, J. *J. Med. Chem.* **1991**, *34*, 1925. Patick, A.; Hongmei, M.; Markowitz, M.; Ho, D.; Webber, S. *Proc. 2nd Nat. Conf. Human Retroviruses and Related Infections* **1995**, *abstr. 184*, 88. Shetty, B. V.; Kosa, M. B.; Khalil, D. A.; Webber, S. *Antimicrob. Agents Chemother.* **1996**, *40*, 110.

(2) Marzoni, G.; Kaldor, S. W.; Trippe, A. J.; Shamblin, B. M.; Fritz, J. E. *Synth. Commun.* **1995**, *25*, 2475.

(3) (a) Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) The author would like to thank Mr. M. Shore for development of this conversion.

(4) The ratio was determined by isolation of **4** and its diastereomer at the carbinol center.

(5) Quenching of the reaction under two-phase conditions (2 N aqueous HCl) resulted in **4** (after reduction) that was racemic.

(6) The chiral assay was performed on a Pirkle (S,S)-Whelk O1 4.6 × 250 mm column. Eluant: 4/4/92 IPA/CH_2Cl_2/hexane. Flow: 1.5 mL/min. Detector: 254 nm. Retention times: **4**, 53 min; **ent-4**, 57 min; diastereomer 1, 37 min; diastereomer 2, 48 min.

(7) Houpis, I. N.; Molina, A.; Reamer, R. A.; Lynch, J. E.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1993**, *34*, 2593. Gohring, W.; Gokhale, S.; Hilpert, H.; Roessler, F.; Schlageter, M.; Vogt, P. *Chimica* **1996**, *50*, 532. Allen, D. R.; Jenkins, S.; Klein, L.; Erickson, R.; Froen, D. U.S. Patent 5,587,481, 1996 (The Monsanto Company).

(8) Dressman, B. A.; Fritz, J. E.; Hammond, M.; Hornback, W. J.; Kaldor, S. W.; Kalish, V. J.; Munroe, J. E.; Reich, S. H.; Tatlock, J. H.; Shepherd, T. A.; Rodriguez, M. J. U.S. Patent 5,484,926, 1994 (Agouron Pharmaceuticals, Inc.); *Chem. Abstr.* **1994**, *123*, 256539v.

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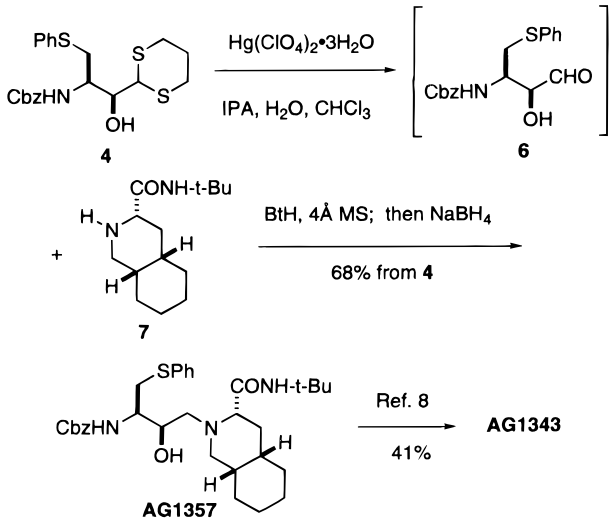
unstable aldehyde generally was not isolated, but was used immediately in the subsequent reductive amination. The use of MeOH in place of IPA in this reaction gave almost exclusively the dimethyl acetal **8**.



Reductive amination of crude **6** with perhydroisoquinoline **7** was also studied under a variety of conditions ($NaCNBH_3$; $NaBH_4$; pyr•BH_3; Ti(O-*i*-Pr)$_4$, $NaBH_4$).[12] These methods were unsatisfactory due to low yields of AG1357 and the large amounts of diol **9** (13−26%) formed as a byproduct through direct reduction of aldehyde **6**. It was found that the method of Katritzky (benzotriazole, 4 Å MS; then $NaBH_4$) was most efficient, resulting in an overall yield of AG1357 of 74% from **4** (corrected for the enantiomeric purity of **4**).[12c] The only byproduct isolated in this reaction was diol **9**. AG1357 has previously been converted to AG1343 in two steps and 41% yield, thus completing a formal four-step synthesis of AG1343.[8] The overall yield for this synthesis of AG1343 is 21% from *N*-Cbz-*S*-Ph-cysteine (**1**).

Experimental Section

In general, ^{1}H NMR data were collected on a GE QE 300 MHz spectrometer. Infrared spectra were taken on a MIDAC FTIR, model number 101280-1. High-resolution mass spectrometry was performed on a VG Analytical 70SEZAB mass spectrometer. Optical rotations were observed using a Jasco DIP-370 digital polarimeter. Melting points are uncorrected.

(1*S*,2*R*)-2-[(Benzyloxycarbonyl)amino]-1-[2-(1,3-dithianyl)]-3-(phenylthio)-1-propanol (4). *N*-Methylmorpholine (12.2 g, 13.3 mL, 0.121 mol) was added slowly to a cold (−20 °C) suspension of *N*-Cbz-*S*-phenylcysteine (40 g, 0.121 mol) in acetonitrile (242 mL) under Ar, keeping the internal temperature below −15 °C, giving a clear solution. Pivaloyl chloride (14.6 g, 14.9 mL, 0.121 mol) was added rapidly. There was a mild exotherm from −20 to −15 °C, and a white precipitate formed. After 1 h at −25 to −15 °C, a 40 wt % solution of dimethylamine in water (13.6 g, 15.2 mL, 0.121 mol) was added, giving a clear solution. After 1 h at −25 to −15 °C, 2 N aqueous HCl (80 mL) was added, and the mixture was warmed to ambient temperature. The acetonitrile was removed *in vacuo*. Methyl *tert*-butyl ether (300 mL) was added to the residue, and the layers were separated. Water (150 mL) and 50% aqueous NaOH (10 mL) were added to the organic layer, and the mixture was stirred vigorously for 1 h. The layers were separated, and water (150 mL) and 50% aqueous NaOH (10 mL) were added to the organic layer. After stirring vigorously for 30 min, the layers were separated and the organic layer was washed with H_2O (150 mL). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give crude amide **2b** as a colorless oil (44.4 g, 102%). This material contained 4.4 wt % methyl *tert*-butyl ether (determined by integration of the ^{1}H NMR spectrum), giving a corrected yield of 98%. The enantiomeric excess was determined to be 88% by analysis on a Pirkle (S,S)-Whelk-O1 column. A portion of this material was used in the next step: $[\alpha]_D^{22}$ +8.8° (*c* 0.0202, $CHCl_3$); IR (thin film) 3281, 2936, 1717, 1645, 1499, 1254, 1044, 741, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.19 (m, 10 H), 5.78 (br d, J = 8.4 Hz, 1 H), 5.12 (s, 2 H), 4.91 (q, J = 7.7 Hz, 1 H), 3.24 (d, J = 5.6 Hz, 2 H), 2.94 (s, 3 H), 2.86 (s, 3 H); HRMS calcd for $C_{19}H_{22}N_2O_3S_1$ + Cs 491.0405, found 491.0389.

n-BuLi (2.5 M in hexanes, 139 mL, 0.348 mol) was added to a cold (−10 °C) solution of 1,3-dithiane (41.8 g, 0.348 mol) in THF (873 mL) under Ar, keeping the internal temperature below −1 °C, giving a yellow solution. After 1 h, a solution of crude amide **2b** (41.56 g, 0.116 mol) in THF (233 mL) was added. After 30 min, a solution of HOAc (56 g, 53 mL, 0.928 mol) in THF (102 mL) was added, giving a thick mixture. This mixture was warmed to ambient temperature, H_2O (233 mL) was added, and the THF and hexanes were removed *in vacuo*. The residue was partitioned between EtOAc (1.2 L) and H_2O (480 mL). The organic layer was washed with H_2O (1 × 480 mL) and brine (1 × 240 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give ketone **3** as a yellow oil. The crude ketone **3** was dissolved in MeOH/THF (195 mL/98 mL), cooled to 4 °C under Ar, and $NaBH_4$ (2.2 g, 0.0580 mol) was added in portions (gas evolution! foaming!). After 15 min, the MeOH/THF was removed *in vacuo*. The residue was diluted with EtOAc (1.2 L), washed with half-saturated brine (2 × 480 mL) and brine (1 × 240 mL), and dried ($MgSO_4$). This mixture was filtered and concentrated *in vacuo* to a yellow oil. This oil was dissolved in EtOAc (93 mL) and heated to 60 °C, and hexanes (113 mL) was added. Crystallization began, and the mixture was allowed to cool to ambient temperature. More hexanes (166 mL) was added, and the mixture was aged at ambient temperature overnight. The mixture was filtered, and the cake was washed with EtOAc/hexanes (25/75, 2 × 20 mL) and hexanes (2 × 20 mL). The white solid was dried *in vacuo* (air sweep, ambient temperature) to give 34.76 g (70% from *N*-Cbz-*S*-phenylcysteine (**1**)) of alcohol **4**. The enantiomeric excess of **4** was determined to be 83% and the syn/anti ratio was 98/2, both determined by chiral HPLC on a Pirkle (S,S)-Whelk-O1 column: mp 74−77 °C; $[\alpha]_D^{22}$ −48.1° (*c* 0.0146, $CHCl_3$); IR (thin film) 3414, 2901, 1705, 1701, 1512, 1240, 1217, 1088, 1026, 752, 696 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 7.40−6.87 (m, 10 H), 5.19 (br d, J = 9.2 Hz, 1 H), 5.07 (br s, 2 H), 4.72 (m, 1 H), 4.07 (d, J = 8.4 Hz, 1 H), 3.47 (d, J = 8.8 Hz, 1 H), 3.04 (m, 2 H), 2.69 (br s, 1 H), 2.44 (t, J = 11.4 Hz, 1 H), 2.21 (t, J = 11.4 Hz, 1 H), 1.87 (m, 2 H), 1.41 (m, 1 H), 1.24 (m, 1 H); HRMS calcd for $C_{21}H_{25}N_1O_3S_3$ + Cs 568.0051, found 568.0033.

[3*S*-(3*R,4a*R**,8a*R**,2′*S**,3′*S**)]-*N*-(1,1-Dimethylethyl)-decahydro-2-[2′-hydroxy-3′-[(benzyloxycarbonyl)amino]-4′-(phenylthio)butyl]-3-isoquinolinecarboxamide (AG1357).**

(9) (a) MeI, H_2O: Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1977**, 68. (b) $HgCl_2$: Corey, E. J.; Boch, M. G. *Tetrahedron Lett.* **1975**, 2643. Seebach, D.; Beck, A. K. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 316. (c) CAN: Ho, T.-L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791. (d) $NaIO_4$, H_2O: Carlson, R. M.; Helquist, P. M. *J. Org. Chem.* **1968**, *33*, 2596. Carey, F. A.; Dailey, O. D., Jr., Hernandez, O.; Tucker, J. R. *J. Org. Chem.* **1976**, *41*, 3975. (e) OHCCOOH, HOAc, HCl: Muxfeldt, H.; Unterweger, W.-D.; Helmchen, G. *Synthesis* **1976**, 694. (f) CuO, $CuCl_2$: Stutz, P.; Stadler, P. A. *Org. Synth.* **1977**, *56*, 8. (g) DDQ: Mathew, L.; Sankararaman, S. *J. Org. Chem.* **1993**, *58*, 7576. (h) $Hg(ClO_4)_2$•$3H_2O$: Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743.

(10) Other one-carbon homologating agents which were studied for the conversion of **1** to **6** were benzothiazole[11] and bis(methylthio)methane. In the former case, the conditions for unmasking the aldehyde ($MeOSO_2F$; aqueous K_2CO_3) proved not to be amenable to scale. Use of MeI was ineffective. In the latter case, the intermediate corresponding to **4** was an oil, making separation of the diastereomers at this point difficult on large scale. For the use of 2-(trimethylsilyl)thiazole as a one-carbon homologating agent in a related system, see: Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Tedshaw, S.; Spurden, W.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656.

(11) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 5,9.

(12) (a) pyr•BH_3: Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995. Moormann, A. E. *Synth. Commun.* **1993**, *23*, 789. (b) Ti(O-*i*-Pr)$_4$, $NaBH_4$: Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928. (c) Benzotriazole, 4 Å MS, $NaBH_4$: Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225.

Mercuric perchlorate trihydrate (20.9 g, 0.0460 mol) was added to a vigorously stirred mixture of dithiane **4** (10.0 g, 0.0230 mol) in isopropyl alcohol/$CHCl_3$/H_2O (3/6/1, 200 mL) at ambient temperature. After 1 h, the mixture was filtered, and the cake was washed with $CHCl_3$ (3 × 100 mL). The combined mother liquors and filtrates were washed with half-saturated brine (2 × 100 mL), saturated aqueous $NaHCO_3$ (1 × 100 mL), and brine (1 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give **6** as a colorless oil. This oil was dissolved in THF (90 mL) and used directly in the subsquent reductive amination.

(3*S*,4a*S*,8a*S*)-3-*N*-(*tert*-Butylcarbamoyl)decahydroisoquinoline (5.5 g, 0.0230 mol), benzotriazole (2.7 g, 0.0230 mol), and 4 Å molecular sieves (7.9 g) were added to a solution of crude aldehyde **6** in THF (90 mL) at ambient temperature. After 17 h, $NaBH_4$ (0.87 g, 0.0230 mol) was added, and the mixture was stirred at ambient temperature. After 25 h further, the mixture was filtered through Celite (THF wash) and concentrated *in vacuo*. The residue was dissolved in EtOAc (300 mL) and washed with 1 N aqueous HCl (1 × 100 mL), H_2O (1 × 100 mL), saturated aqueous $NaHCO_3$ (1 × 100 mL), and brine (1 × 100 mL). The organic layer was dried (Na_2SO_4) and purified by flash chromatography (50/50 EtOAc/hexanes) to give AG1357 as a white foam (10.06 g, 77% from **4**). This material contained 12 wt % benzotriazole, giving a corrected yield of 8.85 g (68% from **4**). Further correction for the enantiomeric purity of **4** (83% ee) gave a corrected yield of AG1357 of 74% from **4**. A small portion of this mixture was purified further to afford pure AG1357. Analytical data (IR ^{1}H NMR, elemental analysis) conformed to that previously reported.[8]

Acknowledgment. The author would like to thank Drs. B. Borer and K. Albizati for helpful advice and encouragement throughout this work. The author would also like to thank Mr. J. Shanley for supplies of amide **2a**.

Supporting Information Available: ^{1}H NMR spectrum of compound **4** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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