A Convergent, Scalable Synthesis of HIV Protease Inhibitor PNU-140690

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PNU-140690, an inhibitor of the HIV protease enzyme undergoing clinical evalution as a chemotherapeutic agent for treatment of AIDS, was synthesized by a convergent approach amenable to large-scale preparation in a pilot plant environment. The key step is the aldol addition of nitroaromatic ester (+)-**8** to aldehyde **19e**. The two stereocenters present in the target molecule were each set independently by resolution of enantiomers. Intermediates along the synthetic routes were chosen to maximize opportunities for isolation and purification by crystallization.

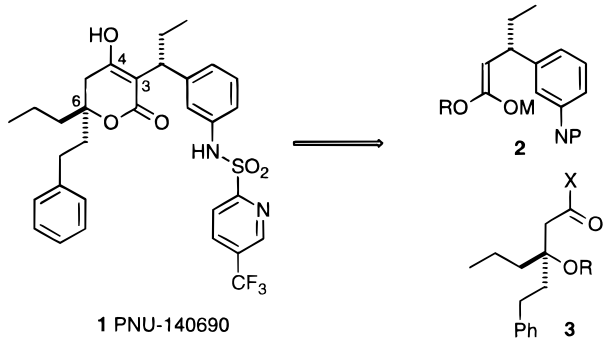
Introduction

PNU-140690 (**1**) is an inhibitor of the HIV protease enzyme and is currently undergoing clinical trials for the treatment of AIDS. This compound emerged from a longstanding research program at Pharmacia & Upjohn to identify effective small molecule inhibitors of the viral protease enzyme.[1] Several HIV protease inhibitors have recently been approved for use by the FDA, all of which are peptidomimetic compounds. PNU-140690 is the first nonpeptide to possess comparable antiviral potency while retaining useful pharmaceutical properties. In addition, it retains useful activity against strains resistant to ritonavir and cross-resistant to other protease inhibitors, suggesting that PNU-140690 could be very valuable when used in combination with a subset of these structurally unrelated drugs.[2]

Availability of an efficient, scalable process for the synthesis of PNU-140690 is vital to its successful clinical development and commercialization. However, its structure and properties pose some unique difficulties. Foremost among these is the poor crystallinity of the target molecule itself and other compounds containing the tertiary alkoxy or acyloxy stereocenter at C_6, restricting opportunities for purification, isolation, and drying. Other challenges include control of stereochemistry at two widely separated asymmetric centers and instability of the dihydropyrone core.

We planned a convergent approach relying on construction of the C_3-C_4 bond of the dihydropyrone ring (Scheme 1). In practice, a Claisen condensation or aldol addition of an enolate represented by **2** with an electrophilic partner **3** was required. In addition to the well-known advantages of convergency, this strategy attracted us because it offered the ability to set each stereocenter independently, simplifying the control of diastereomeric impurities.

Scheme 1



1 PNU-140690

Results and Discussion

A classical resolution to set the C_6 stereocenter, the key feature of the projected electrophile **3**, was planned from the outset of this work. In keeping with our strategy, racemic hydroxy acid **4** was chosen as the resolution "substrate" (Scheme 2). The hydroxy acid synthesis was originally performed in a single step by addition of the dianion of acetic acid to 1-phenyl-3-hexanone. However, yields were higher and more reproducible when done in two steps. Thus, addition of the ketone to a THF solution of the lithium enolate of ethyl acetate while maintaining the temperature at or below −30 °C afforded the ethyl ester **5** in nearly quantitative yield. Higher temperatures resulted in recovery of unreacted 1-phenyl-3-hexanone. Isolation of **5** was unnecessary; instead, after aqueous workup the unpurified ester was directly subjected to saponification with sodium hydroxide in methanol. Hydroxy acid (±)-**4** was isolated by standard basic extraction and concentrated to a viscous oil. It was not necessary to remove all of the solvent before doing the resolution.

Resolution of (±)-**4** was achieved by crystallization with norephedrine. Other chiral amines screened for this

(1) (a) Thaisrivongs, S.; Skulnick, H. I.; Turner, S. R.; Strohbach, J. W.; Tommasi, R. A.; Johnson, P. D.; Aristoff, P. A.; Judge, T. M.; Gammill, R. B.; Morris, J. K.; Romines, K. R.; Chrusciel, R. A.; Hinshaw, R. R.; Chong, K.-T.; Tarpley, W. G.; Poppe, S. M.; Slade, D. E.; Lynn, J. C.; Horng, M.-M.; Tomich, P. K.; Seest, E. P.; Dolak, L. A.; Howe, W. J.; Howard, G. M.; Schwende, F. J.; Toth, L. N.; Padbury, G. E.; Wilson, G. J.; Shiou, L.; Zipp, G. L.; Winkinson, K. F.; Rush, B. D.; Ruwart, M. J.; Koeplinger, K. A.; Zhao, Z.; Cole, S.; Zaya, R. M.; Kakuk, T. J.; Janakiraman, M. N.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 4349−4353. (b) Judge, T. M.; Phillips, G.; Morris, J. K.; Lovasz, K. D.; Romines, K. R.; Luke, G. P.; Tulinsky, J.; Tustin, J. M.; Chrusciel, R. A.; Dolak, L. A.; Mizsak, S. A.; Watt, W. A.; Morris, J.; VanderVelde, S. L.; Strohbach, J. W.; Gammill, R. B. *J. Am. Chem. Soc.* **1997**, *119*, 3627−3628.

(2) Chong, K.-T.; Pagano, P. J. *Antimicrob. Agents Chemother.* **1997**, *41*, 2367−2373.

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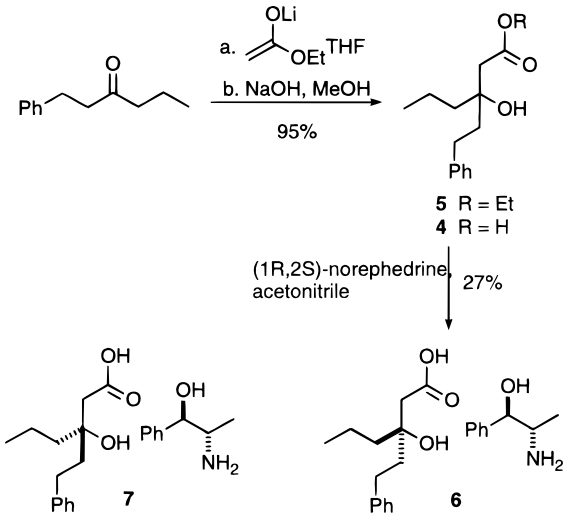
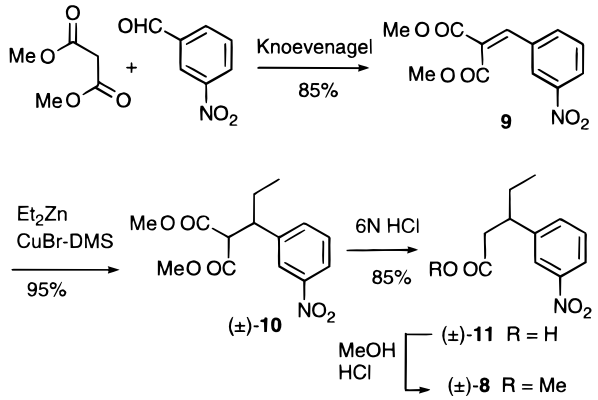
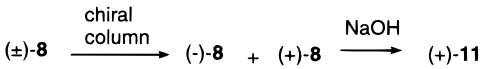
Scheme 2



Scheme 3



Scheme 4



purpose included α-methylbenzylamine, phenylglycinol, ephedrine, and sparteine. (1*R*,2*S*)-Norephedrine crystallized with the stereoisomer of **4** needed for PNU-140690 synthesis. This was determined first by chemical correlation (vide infra) but was later confirmed by X-ray structure determination of the diasteromeric salt **7**. The first set of conditions for the resolution consisted of reaction of the racemate (10 mL/g in acetonitrile) with 1 equiv of norephedrine followed by two recrystallizations from acetonitrile, affording the desired salt **6** in about 35% yield. However, the level of chiral purity was inconsistent. Eventually, we determined that chiral purity and filterability were much more reproducible when the salt was formed from only 0.5 equiv of the amine, albeit in lower yield. Almost all of the yield loss was incurred during the salt formation; each recrystallization from acetonitrile comes at the expense of only 1−2% yield. Solubility measurements of **6** and its diastereomer **7** suggested that toluene and methylene chloride might also be appropriate solvents for salt formation. However, we were not able to form tractable salts in either of these solvents. Efforts to improve the yield by adjusting concentration and temperature during the salt formation were marginally successful. While colder temperature did increase the yield, enantiopurity suffered. Decreasing the volume improved the yield without sacrificing enantiomeric excess, but volumes lower than 5 mL/g of (±)-**4** became unstirrable. In the preferred variant of the procedure, the salt formation is done at a concentration of 5 mL/g and 0 °C to maximize yield and recrystallized twice at 7 mL/g and room temperature to achieve the desired optical purity (>99:1). (1*R*,2*S*)-Norephedrine recovered by standard acid/base extraction techniques can be reused.

Earlier syntheses of PNU-140690 have incorporated the nitrogen substituent at the meta position of the phenyl ring as a dibenzyl-protected aniline,[1] as did an early version of the aldol process described here. Because of its susceptibility to oxidation, lack of crystallinity, and the high mass of the protecting groups, we wanted to replace the dibenzyl aniline moiety with another aniline surrogate, preferably a nitro group. Toward this end, we sought an efficient synthesis of (*R*)-**8**. In our first approach to **8**, we wished to pursue a Michael addition to an unsaturated ester, but earlier work in our group had shown that the nitro group inhibited the copper-catalyzed addition of ethyl Grignard or ethyl zinc reagents to methyl 3-nitrocinnamate. We surmised that the addition might be facilitated by an additional carboxy group. Thus, we prepared dimethyl 3-nitrobenzalmalonate (**9**) by Knoevenagel condensation (Scheme 3). This compound, indeed, was found to undergo Michael addition with a variety of copper reagents including the Knochel reagent,[3] copper-catalyzed Grignard addition, and most simply and in highest yield with copper bromide catalyzed addition of diethyl zinc, giving the racemic malonate **10**. Hydrolysis and concomitant decarboxylation readily produced the desired 3-(*m*-nitrophenyl)-propionic acid **11**, which in turn was converted to the methyl ester **8** by Fischer esterification.

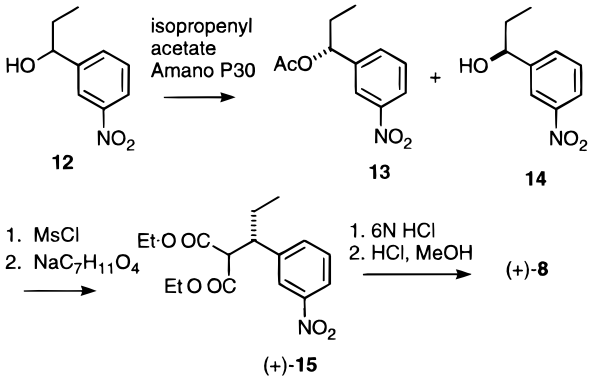
Attempts at resolution of the acid with a variety of chiral amines resulted in only moderate yields of the diastereomerically enriched salts. Wishing to rapidly obtain samples of key coupling products derived from (*R*)-**8**, we decided to separate the isomers[4] by preparative chiral column chromatography, and this was readily achieved (Scheme 4). Once coupling of this material to the left-hand portion of the molecule was successfully demonstrated (see below), an alternative preparation of (+)-**8** was sought. 1-(*m*-Nitrophenyl)propanol (**12**) is readily available by reduction of the corresponding propiophenone. Acylation of this material with isopropenyl acetate in the presence of Amano P30 lipase results in a nearly quantitative conversion of the (*R*)-alcohol to its acetate, leaving the nearly enantiomerically pure alcohol in close to 50% weight yield (Scheme 5). These compounds were readily separated chromatographically. Alcohol **14** was converted to the mesylate and reacted with sodium diethyl malonate to give the diester (+)-**15**. Hydrolysis−decarboxylation and reesterification gave (+)-**8**.

Of the reactions examined for formation of the key C_3-C_4 bond, the more aggressive Claisen condensation approach was plagued by two fundamental problems. The first was reactivity: the presence of the tertiary β-hydroxyl group made preparation of active acylating agents

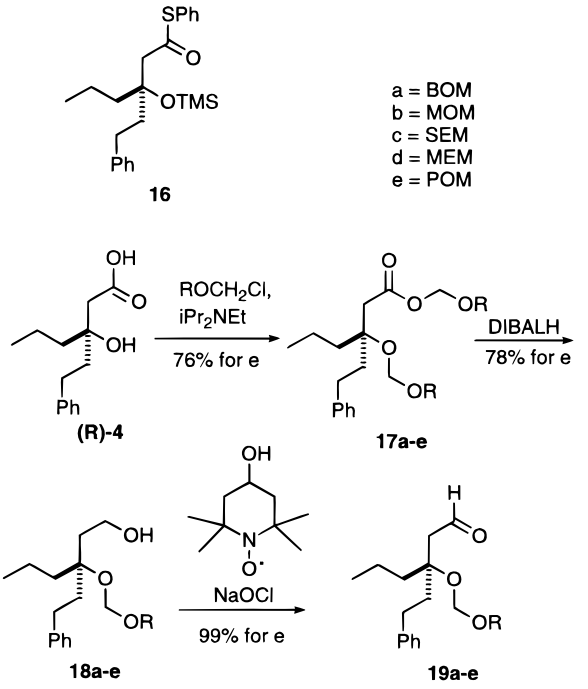
(3) (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 7. (b) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5431.

(4) The assignment of stereochemistry was achieved by correlation of the (+)-isomer with (*R*)-3-[*m*-(dibenzylamino)phenyl]propanoic acid methyl ester. This material had previously been converted to PNU-140690.

Scheme 5



Scheme 6



such as the acid chloride very difficult because of the possibility of elimination or retroaldol. The most successful acylating agent was the thiophenyl ester **16**[5] (Scheme 6), which could be prepared by reacting the acid with carbonyldiimidazole and thiophenol followed by silylation.[6] However, this electrophile is not synthetically useful in this situation because of the second and more difficult problem: the acidity of the product β-keto esters. The enolate quenching byproduct limited conversion to 50%. Additional base served only to deprotonate the thioester, thus deactivating it as an electrophile. In principle, the conversion problem could be avoided by acylating a substituted malonate derivative instead of a simple enolate, but doing so exacerbated the reactivity problem. The problem might also be solved by acylating with electrophiles that would be expected to form stable tetrahedral intermediates (*N*-methoxy-*N*-methylamides[7] or acyl cyanides[8]), but these either lacked sufficient reactivity or proved unstable.

An aldol process addresses both the reactivity and product acidity problems encountered in the attempted direct acylation chemistry. These benefits come at the price of having to adjust the oxidation state sometime after coupling the two halves of the molecule. The aldehydes **19** required for this study were prepared by derivatization of both the acid and alcohol functional groups of acid (*R*)-**4**, reduction of the resulting ester to the primary alcohol with diisobutylaluminum hydride, and tetramethylpiperidinyloxy radical (TEMPO) catalyzed sodium hypochlorite oxidation[9] to the aldehyde. This protocol and several variations thereof were used without success to make derivatives protected by a silyl ether as in **16**. However, chloromethyl ethers reacted readily under standard conditions, and the benzyloxymethyl- (BOM), methoxymethyl- (MOM), [2-(trimethylsilyl)ethoxy]methyl- (SEM), and (methoxyethoxy)methyl- (MEM) ether derivatives were prepared in this manner. Attempts to prepare the corresponding allyl or benzyl ethers failed. Curiously, with oxymethyl esters it was not possible to stop the reduction reactions at the aldehyde oxidation step even at −78 °C, a process that worked well with the corresponding ethyl ester compounds.

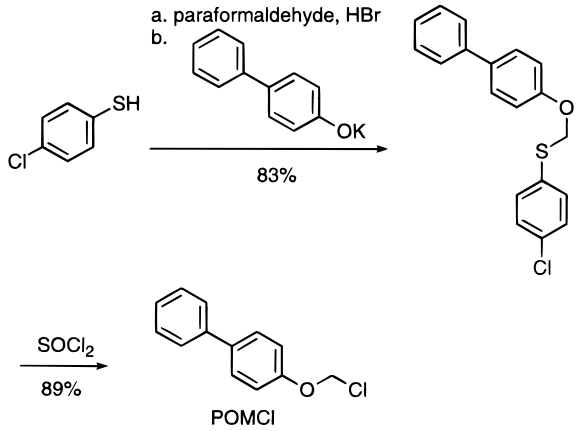
Unfortunately for our purposes, none of the aldehydes **19a**−**d** are crystalline, nor are the ester and alcohol intermediates used in their preparation. The aldehydes themselves also displayed a tendency to self-condense during silica gel chromatography, the extent of dimerization related both to the bulkiness of the protecting group and residence time on the column. In general, it was not possible to remove the dimer once formed from the aldehyde because of the similarities of polarity between the two. The presence of varying amounts of dimer in samples of aldehyde made accurate determination of the yield in and optimization of the subsequent aldol reactions very difficult.

The [(*p*-phenylphenyl)oxy]methyl (POM) ether was invented to induce crystallinity in the aldehyde and thereby solve the purification problem. Of all the attempted protections or derivatizations of the tertiary alcohol in **4**, only base-promoted reactions with alkoxymethyl chlorides have worked well. To the extent that crystallinity might be expected to be related to the melting point of the alkoxy group employed, 4-phenylphenol (mp 165−167 °C) was selected for incorporation into a new protecting group.[10] The previously unknown 1-(chloromethoxy)-4-phenylbenzene (POMCl) was synthesized in 74% yield from *p*-chlorothiophenol according to a literature method as shown below (Scheme 7).[11]

Derivatization of **4** with POMCl required more stringent conditions than those used for reaction with simpler alkoxymethyl chlorides. Esterification proceeded readily, but protection of the tertiary hydroxy group required reaction with an excess of POMCl and diisopropylethylamine for 5 h in refluxing toluene. Under these conditions, POMCl slowly decomposes to 4-phenylphenol and bis(4-phenylphenoxy)methane. Bases examined for this

(5) Damon, R. E.; Luo, T.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, *32*, 2749.
(6) Gais, H. J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 244.
(7) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3816. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993.
(8) Hunig, S.; Schaller, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 36−49.
(9) Hewitt, B. D. PCT Int. Appl. WO 9516698 A1, 1994; *Chem. Abstr.* **1994**, *123*, 314263.
(10) Other noncrystalline aryloxyethers have been used as protecting groups for tertiary alcohols. See: (a) Masaki, Y.; Iwata, I.; Mukai, I.; Oda, H.; Nagashima, H. *Chem. Lett.* **1989**, 659−662. (b) Loubinoux, B.; Coudert, G.; Guillaumet, G. *Tetrahedron Lett.* **1981**, *22*, 1973−1976.
(11) Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1983**, *B37*, 93−96.

Scheme 7

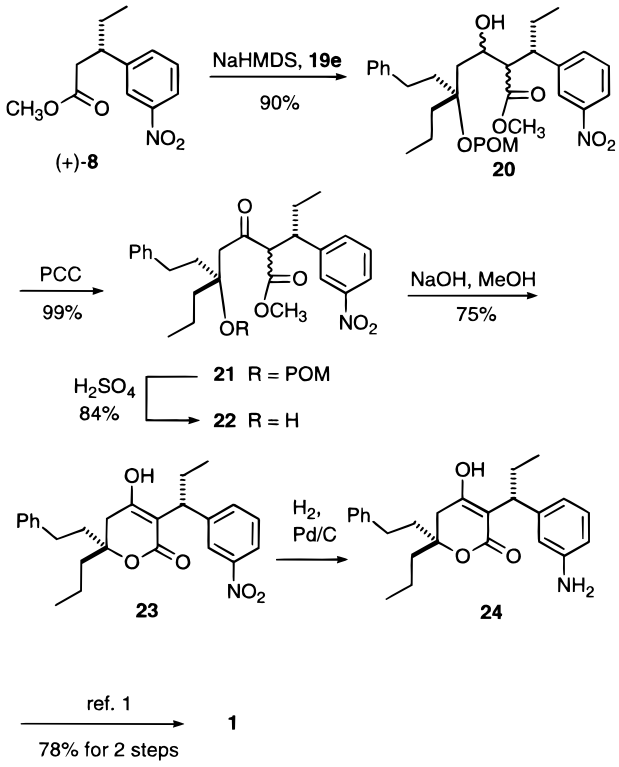


reaction included potassium carbonate, triethylamine, tributylamine, diethylaniline, dimethylaniline, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), molecular sieves, and no base at all, but all were inferior to diisopropylethylamine. The crude product could be precipitated from the reaction mixture by addition of methanol. The major contaminant was the diphenoxymethane impurity, which was conveniently removed by filtration in the next step.

Reduction of ester **17e** with diisobutylaluminum hydride in toluene as above proceeded smoothly. No other reducing agents were examined. Excess reagent was quenched with acetone, and the aluminum salts were removed by extraction with aqueous citric acid. After a sodium hydroxide wash to remove the 4-phenylphenol byproduct of the reduction, alcohol **18e** was crystallized from methylene chloride/hexane. The bleach/TEMPO oxidation also proceeded as expected. The crude product solution was subjected to a filtration through magnesol. Displacement of methylene chloride with hexane resulted in crystallization of the desired aldehyde **19e** (mp 47.0−48.5 °C) in an analytically pure state. Thus, use of the POM protecting group allowed for preparation, purification, and isolation of a suitably functionalized aldehyde without chromatography. Aldehyde **19e** could also be stored for weeks without any evidence of dimerization or other degradation.

With the two coupling partners in hand, we turned to the crucial aldol addition reaction. Enolization of ester (+)-**8** with lithium diisopropylamide in tetrahydrofuran solution led to formation of a dark brown color, and the subsequent reaction with aldehyde **19a** resulted in low conversion to the desired aldol adducts and significant dimerization of the aldehyde. Supposing that the unsatisfactory result was due to electron transfer from the amide base to the nitroaromatic, we chose to attempt enolization with the weaker base, and less effective one-electron reductant, lithium hexamethyldisilazide. The yield rose to 76%. Interestingly, at this time a paper by Black appeared reporting the metalation of 2,4-difluoronitrobenzene.[12] In this study, hexamethyldisilazide bases, especially with sodium or potassium counterion, were far superior to lithium diisopropylamide, which again was prone to one-electron-transfer reactions. Application of sodium hexamethyldisilazide to our system resulted in a slight increase in yield relative to the lithium case.

Scheme 8



As discussed above, full optimization and accurate yield measurement for the aldol reaction were hindered at first by lack of aldehyde purity. With the availability of POM-protected aldehyde **19e**, application of our best conditions afforded aldols **20** as a mixture of four diastereomers in 90% yield (Scheme 8). The mixture could be carried directly into the next reaction after an aqueous workup. Attempted reaction at −25 °C instead of −80 °C resulted in extensive aldehyde decomposition from dimerization and loss of the POM group.

Pyridinium chlorochromate (PCC) on basic alumina and the Swern oxidation were investigated for conversion of the aldols to β-keto esters in an earlier version of this chemistry. PCC was chosen because it does not require low temperature, is operationally simpler, and does not generate odor. Application to aldols **20** resulted in quantitative conversion to β-keto ester **21** as a mixture of two diastereomers (epimers at the labile C_3 center). After removal of the chromium salts by filtration through magnesol, the unpurified product was carried directly into the next reaction, acidic hydrolysis of the POM protecting group. This was accomplished by treatment with sulfuric acid in THF/methanol solution at room temperature.[13] It is notable that these conditions do not result in appreciable elimination of the tertiary alcohol to form a mixture of unsaturated ketones, a facile decomposition pathway seen with many of the intermediates described in this paper. Once again, the unpurified product **22** could be carried into the next reaction following an aqueous workup to remove the 4-phenylphenol byproduct.

Saponification of ester **22** leads directly to the lactonized intermediate **23**. Cyclization appears to occur spontaneously under the basic reaction conditions as

(12) Black, W. C.; Guay, B.; Scheuermeyer, F. *J. Org. Chem.* **1997**, *62*, 758−760.

(13) Shih, T.; Thomas, L.; Wyvratt, M. J. *J. Org. Chem.* **1987**, *52*, 2029−2033.

indicated by our failure to detect any intermediates by TLC or HPLC. That the reaction is truly a saponification followed by cyclization rather than direct lactonization of the hydroxy ester is suggested by the inability of potassium *tert*-butoxide to mediate the closure. Use of sodium hydroxide in THF,[14] conditions used successfully for several related substrates, resulted in unexpectedly high levels of decarboxylation to form an open-chain ketone. Use of an alcoholic medium led to improvement, but there was little difference over the series methanol−ethanol−2-propanol. After extensive experimentation, reaction with 1.5−2 equiv of sodium hydroxide in methanol at 0 °C was found to produce the optimal yield of lactone **23**. The reaction takes 3 days to go to completion at this temperature, but the value of this late intermediate provides justification. Upon completion, neutral species are removed by hexane extraction, the pH of the aqueous methanol layer is adjusted, and the product is extracted into methylene chloride. Upon concentration and addition of diethyl ether, analytically pure **23** crystallizes in 75% yield. Lactone **23** is the first crystalline intermediate since aldehyde **19e**; its efficient purification by crystallization is significant in light of the four synthetic steps performed. Comparison of NMR spectra recorded in different solvents reveals that the proportions of **23** existing in the enol tautomer shown and the mixture of diastereomeric C_3 keto tautomers varies, with a tendency to exist as the enol in protic media.

Hydrogenation of nitroaromatic **23** under mild conditions quantitatively gives aniline **24**, the previously reported penultimate intermediate. Intersection with this intermediate conclusively proves the C_6 stereochemistry obtained from the resolution of (±)-**4**. It is worthy of note that application of the same sulfonylation and purification conditions afforded a 78% yield of analytically pure **1**. This yield is by far the highest yet attained for this step, roughly 20% above what was routinely achieved earlier when intermediates were not chromatographically purified. Much of this improvement is attributable to the high-quality **24** derived from this new route.

Conclusion

A convergent route for preparation of PNU-140690 (**1**) amenable to scale-up has been developed. The new route sets each of the two stereocenters present in the final target separately, allowing for easy control over the level of diastereomeric impurities. It uses relatively cheap raw materials and reagents that do not pose severe hazards for large-scale manufacture, although an evaluation of toxicity associated with POMCl must still be investigated. Notable features include a resolution to set the stereochemistry of the tertiary hydroxyl group at C_6, development of a new (aryloxy)methyl ether protecting group for alcohols useful for inducing crystallinity, successful enolization of ester **8** containing an aryl nitro group, and identification of a crystalline advanced intermediate **23**.

Experimental Section

General Procedures. All reagents were commercially obtained and used as received unless otherwise noted. All nonaqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive liquids or solutions were transferred via syringe or polypropylene cannula. Organic solutions were concentrated by rotary evaporation at ~80 mmHg and less than 60 °C except where noted.

NMR spectra were recorded at 300 and 75 MHz for ^{1}H and ^{13}C, respectively, in $CDCl_3$ unless otherwise noted. Multiplicities for ^{13}C experiments are reported on the basis of DEPT data. Melting points were determined in unsealed capillary tubes and are uncorrected. Elemental analysis and high-resolution mass spectra (HRMS) and optical rotations were obtained from Pharmacia and Upjohn Physical and Analytical Chemistry. The following HPLC method was used: stationary phase, 4.6 X 250 mm Zorbax RX C-8 column; mobile phase A = acetonitrile; mobile phase B = water; gradient from 50:50 A:B to 100:0 A:B over 15 min; flow rate = 2.0 mL/min; UV detection at 254 nm.

Ethyl 3-Hydroxy-3-(2-phenylethyl)hexanoate (5). To a solution of diisopropylamine (32.2 mL, 230 mmol) in THF (240 mL) cooled to −58 °C was added 2.63 M *n*-butyllithium in hexane (87.4 mL, 230 mmol) over 1 h. Ethyl acetate (21.4 mL, 220 mmol) was then added and the reaction mixture stirred for 1 h, during which time the reaction mixture was cooled to −70 °C. 1-Phenylhexan-3-one (35.2 g, 200 mmol) was added slowly over 30 min and the reaction mixture stirred cold for 1 h. The mixture was quenched with aqueous ammonium chloride (100 mL) and warmed to room temperature. The product was extracted into methyl *tert*-butyl ether, dried over $MgSO_4$, and concentrated to give 53.41 g (98%) of **5** as an oil: TLC R_f = 0.71 (30% EtOAc/hexanes); ^{1}H NMR δ 7.28−7.12 (m, 5H), 4.13 (q, 2H, J = 7.1 Hz), 3.60 (s, 1H), 2.73−2.63 (m, 2H), 2.50 (s, 2H), 1.83−1.77 (m, 2H), 1.58−1.53 (m, 2H), 1.41−1.36 (m, 2H), 1.24 (t, 3H, J = 7.1 Hz), 0.93 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 173.0 (s), 143.2 (s), 128.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 125.8 (d), 72.8 (s), 60.6 (t), 42.9 (t), 41.3 (t), 30.1 (t), 17.0 (t), 14.6 (q), 14.2 (q); MS (CI, NH_3) m/z (relative intensity) 282 (100), 264 (63). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.69; H, 9.41.

3-Hydroxy-3-(2-phenylethyl)hexanoic Acid ((±)-4). Ester **5** (200 mmol) was dissolved in methanol (423 mL), and 2 M aqueous NaOH (150 mL, 300 mmol) was added. The reaction mixture was stirred at room-temperature overnight. Methanol was removed in vacuo and the remaining solution acidified with 4 M aqueous HCl. This was extracted into methyl *tert*-butyl ether, dried over $MgSO_4$, and concentrated to give 44.51 g (94%) of (±)-**4** as a yellow oil: TLC R_f = 0.10 (30% EtOAc/hexanes); ^{1}H NMR δ 7.43−7.13 (m, 5H), 2.77−2.62 (m, 2H), 2.06 (s, 2H), 1.87−1.76 (m, 2H), 1.63−1.57 (m, 2H), 1.45−1.31 (m, 2H), 0.93 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 176.9 (s), 141.9 (s), 128.4 (d), 128.3 (d), 125.9 (d), 73.4 (s), 42.7 (t), 41.4 (t), 40.9 (t), 31.9 (t), 17.0 (t), 14.5 (q); MS (CI, NH_3) m/z (relative intensity) 254 (100), 236 (28). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.22; H, 8.68.

(*R*)-3-Hydroxy-3-(2-phenylethyl)hexanoic Acid, (1*R*,2*S*)-Norephedrine Salt (6). Hydroxy acid (±)-**4** (2.83 g, 11.97) was dissolved in acetonitrile (15 mL). (1*R*,2*S*)-(−)-Norephedrine (910 mg, 5.99 mmol, 0.5 equiv) was added and the mixture stirred overnight at room temperature. After approximately 1 h, crystals began to precipitate. The slurry was cooled to 0 °C for 1 h before filtering to collect the crude salt. The solids were washed with 9 mL of cold acetonitrile to give 1.53 g (33%, 92% ee) of crude **6** as white crystalline solids. The solids were slurried in acetonitrile (21 mL) and heated to 70 °C for 30 min. The resulting solution was gradually cooled to room temperature as the product precipitated. After 2 h at room temperature, the product was collected by vacuum filtration and washed with acetonitrile (21 mL). The recrystallization from acetonitrile was repeated to yield 1.25 g (27%, 98% ee by chiral HPLC analysis) of white crystalline **6**: mp 113−117 °C; ^{1}H NMR (MeOH) δ 7.41−7.08 (m, 10H), 5.18 (s, 5H), 4.98 (d,1H, J = 3.2 Hz), 3.15 (m, 1H), 2.65−2.60 (m, 2H), 2.34 (s, 2H), 1.79−1.73 (m, 2H), 1.56−1.52 (m, 2H), 1.43−1.37 (m, 2H), 1.06 (d, 2H, J = 6.7 Hz), 0.92 (t, 3H, J = 7.1 Hz); ^{13}C NMR (MeOH) δ 181.4 (s),144.6 (s), 142.2 (s), 130.2−129.3 (d), 127.6 (d), 127.1 (d), 74.5 (s), 73.9 (s), 54.0 (d), 46.4 (t), 43.6 (t), 43.4 (t), 31.9 (t), 31.9 (t), 18.6 (t), 15.7 (q), 12.9 (q); MS (CI,

(14) Peterson, J. R.; Miller, C. P. *Synth. Commun.* **1988**, *18*, 949.

NH_3) *m/z* (relative intensity) 388 (25), 254 (30), 236 (7), 152 (100); $[\alpha]^{25}_D$ +16° (*c* 1.0, MeOH). Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.53; N, 3.61. Found: C, 70.99; H, 8.68; N, 3.62.

Dimethyl (3-Nitrobenzal)malonate (9). 3-Nitrobenzaldehyde (75.5 g, 0.50 mol) and dimethyl malonate (70.0 g, 0.53 mol) were added to toluene (200 mL) and cyclohexane (150 mL). The mixture was treated with benzoic acid (2.0 g, 0.017 mol) and piperidine (2.5 mL, 2.15 g, 0.025 mol) and then heated under reflux, collecting the evolved water in a Dean−Stark trap. After 5.5 h, 8.8 mL (0.49 mol) of water was collected. The reaction was then cooled to room temperature and allowed to stand for 16 h. The resultant crystals were collected and washed with methanol, giving dimethyl (3-nitrobenzal)malonate (**9**) (86.5 g, mp 98.5−99.4 °C). The filtrate and washings from these crystals were concentrated and crystallized from methanol, giving additional dimethyl (3-nitrobenzal)malonate (21.1 g): TLC R_f = 0.34 (20% EtOAc/hexane); ^{1}H NMR δ 3.88 (s, 3H), 3.90 (s, 3H), 7.59 (t, 1H), 7.73 (br d, 1H), 7.79 (s, 1H), 8.26 (br d,1H), 8.31 (br s, 1H); IR (drift) 1722, 1535 cm^{-1}; UV λ_{max} 262 nm (25200, 95% EtOH). Anal. Calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28. Found: C, 54.23; H, 4.18; N, 5.27.

(+)-Dimethyl 1-[1-(3-Nitrophenyl)propyl]malonate ((+)-10). Dimethyl (3-nitrobenzal)malonate (**9**) (105.6 g, 0.399 mol) was dissolved in dry THF (525 mL) and the solution treated with cuprous bromide methyl sulfide (16.3 g, 0.05 mol) and cooled to −10 °C under a nitrogen atmosphere. To this was added (1 h) diethylzinc in hexane (1 M, 450 mL, 0.45 mol). After 2 h, the solution was treated dropwise with saturated aqueous ammonium chloride (250 mL). The reaction was then poured into ethyl acetate and extracted with hydrochloric acid (1 N) and saturated aqueous sodium chloride. The ethyl acetate solution was dried (sodium sulfate) and concentrated under vacuum to give dimethyl 1-(3-nitrophenyl)propylmalonate ((+)-**10**) (113.9 g). A sample of this material was recrystallized from methanol (mp 84.6−84.9° C): TLC R_f = 0.38 (20% EtOAc/hexane); ^{1}H NMR δ 0.735 (t, 3H), 1.6−1.9 (m, 2H), 3.42 (dt, 1H), 3.47 (s, 3H), 3.71 (d, 1H), 3.79 (s, 3H), 7.48 (t, 1H), 7.55 (br d, 1H), 7.79 (s, 1H), 8.11 (br d, 1H); IR (drift) 1723, 1528 cm^{-1}; UV λ_{max} 262 nm (8010, 95% EtOH). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.92; H, 5.82; N, 4.78.

3-(3-Nitrophenyl)pentanoic Acid ((±)-11) and Its Cyclohexylamine Salt. Dimethyl 1-(3-nitrophenyl)propylmalonate ((±)-**10**) (97 g, 0.331 mol) was treated with 1 N hydrochloric acid (1 L) and the mixture stirred vigorously and heated under reflux (19 h). The reaction was then cooled and extracted two times with methylene chloride. The combined methylene chloride solutions were dried (sodium sulfate) and concentrated under vacuum, leaving 3-(3-nitrophenyl)pentanoic acid (±)-**11** (71.38 g) as a pale brown solid: TLC R_f = 0.10 (20% EtOAc/hexane); ^{1}H NMR δ 0.804 (t, 3H), 1.57−1.88 (m, 2H), 2.56−2.80 (m, 2H), 3.5−3.2 (m, 1H), 7.4−7.55 (m, 2H), 7.97−8.12 (m, 2H); IR (drift) 3090, 3078, 3045, 2967, 2932, 1709, 1528, cm^{-1}; UV λ_{max} 263 nm (7760, 95% EtOH). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 58.97; H, 5.85; N, 6.23.

The solid was dissolved in ethyl acetate and the solution treated with cyclohexylamine (31.7 g, 0.32 mol). After the solution was allowed to stand for 16 h, the crystals of 3-(3-nitrophenyl)pentanoic acid cyclohexylamine salt were collected (96.13 g, mp 143.8−144.6° C): IR (drift) 2937, 1632, 1528, 1380, cm^{-1}; UV λ_{max} 264 nm (7690, MeOH). Anal. Calcd for $C_{11}H_{13}NO_4.C_6H_{13}N$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.42; H, 8.12; N, 8.63.

(+)-3-(3-Nitrophenyl)pentanoic Acid Methyl Ester ((+)-8). To a solution of (±)-3-(3-nitrophenyl)pentanoic acid (**11**, 30.21 g, 135 mmol) in methanol (250 mL) was added concentrated sulfuric acid (0.6 mL). The resulting mixture was heated to reflux for 3 h. Upon cooling, the mixture was partitioned between ethyl acetate and sodium bicarbonate (5% aqueous). The aqueous layer was separated and back-extracted with two additional portions of ethyl acetate. The combined organic phases were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated to give the title compound: TLC R_f = 0.54 (20% EtOAc/hexane); ^{1}H NMR δ 0.80 (t, 3H), 1.56−1.83 (m, 2H), 2.55−2.75 (m, 2H), 3.05−3.2 (m, 1H), 3.57 (s, 3H), 7.4−7.55 (m, 2H), 8.03−8.12 (m, 2H).

Chiral Separation of 3-(3-Nitrophenyl)pentanoic Acid Methyl Ester ((±)-8) to (*R*)-3-(3-Nitrophenyl)pentanoic Acid Methyl Ester ((+)-8) and (*S*)-3-(3-Nitrophenyl)-pentanoic Acid Methyl Ester ((−)-8). Aliquots (5.0 mL of 60 mg/mL) of (±)-**8** in the mobile phase were injected onto a 50 × 30 cm (R,R)Whelk-O 1 column (Regis Technologies). The mobile of 10% 2-propanol in heptane was pumped at 50 mL/min at 30 °C, and the eluted products were monitored at 260 nm. Resolution was incomplete after a single pass through the column. The leading and tailing edges of the material eluting from 28 to 40 min was collected and the central portion recycled. Automated iteration of this allowed the processing of 0.25 g/h of racemate. In this manner, (±)-**8** (27.94 g) was resolved to the less polar isomer (−)-**8** (12.1 g, $[\alpha]^{25}_D$ −20.1°) and the more polar isomer (+)-**8** (13.1 g, $[\alpha]^{25}_D$ +18.6°). These materials were found to have 99% and 98.2% ee, respectively, as determined below.

The retention times were 18.9 and 20.5 min for the enantiomers when the racemate was injected onto a 0.46 × 25 cm (R,R)Whelk-O 1 column (Regis Technologies) eluted with 10% 2-propanol in heptane (V/V) at 0.5 mL/min while being observed at 260 nm, ambient temperature.

3-(3-Nitrophenyl)pentanoic Acid ((+)-11) and Its Cyclohexylamine Salt by Hydrolysis of (*R*)-3-(3-Nitrophenyl)pentanoic Acid Methyl Ester ((+)-8). (*R*)-3-(3-Nitrophenyl)pentanoic acid methyl ester ((+)-**8**) (1.15 g, 4.84 mmol) was treated with methanol (25 mL) and 1 N sodium hydroxide (7.2 mL, 7.2 mmol) and the solution stirred for 18 h. The reaction was then concentrated under vacuum and the residue partitioned between ethyl acetate and 1 N hydrochloric acid. The organic layer was dried (sodium sulfate) and evaporated under vacuum to give 3-(3-nitrophenyl)pentanoic acid ((+)-**11**) (1.074 g): $[\alpha]^{25}_D$ = +22.7°; $[\alpha]^{25}_{578}$ = +23.7° (MeOH, *c* = 1.0)

3-(3-nitrophenyl)pentanoic acid ((+)-**11**) (1.074 g) was dissolved in ethyl acetate and treated with cyclohexylamine (0.55 mL). The crystals of 3-(3-nitrophenyl)pentanoic acid cyclohexylamine salt (1.446 g) was collected by filtration: mp 145−7 °C; $[\alpha]^{25}_{578}$ = +12.8° (MeOH, *c* = 1.0)

Resolution of (±)-1-(3-Nitrophenyl)propanol (12) by Conversion to (*S*)-1-(3-Nitrophenyl)propanol (13) and (*R*)-1-(3-Nitrophenyl)propanol Acetate (14). Celite-supported PS-30 lipase (Amano, 24 g) and isopropenyl acetate (22.00 mL, 0.20 mol) was added to (±)-1-(3-nitrophenyl)propanol (**12**, 24.00 g, 0.13 mol) in MTBE (240 mL). The mixture was stirred at 20−25 °C for 2 days. At the end of this time, the catalyst was removed by filtration, the catalyst cake washed with ether, and the mixture concentrated under reduced pressure to give an acetate−alcohol mixture. Separation of the mixture by silica gel chromatography gave **14** (13.03 g) and **13** (10.7 g). Data for **14**: ^{1}H NMR δ 0.91−0.96 (t, 3 H), 1.75−1.87 (m, 2 H), 2.04 (br s, 1 H), 4.72−4.76 (t, 1 H), 7.48−7.53 (t, 1 H), 7.66−7.69 (d, 1 H), 8.10−8.13 (m, 1 H), 8.20−8.21 (m, 1 H); $[\alpha]^{25}_D$ +68.7° (EtOH, *c* = 1). Data for **13**: $[\alpha]^{25}_D$ −33.0° (EtOH, *c* = 1).

(*S*)-1-(3-Nitrophenyl)propanol Mesylate. Diisopropylethylamine (1.07 g, 8.3 mmol) was added to a mixture of (*S*)-1-(3-nitrophenyl)propanol (**14**, 1 g, 5.5 mmol) in methylene chloride (20 mL). The mixture was cooled to −20 °C, and methanesulfonyl chloride (0.69 g, 6.02 mmol) was added. The reaction was held at −20 °C for 10 min and then held at 0 °C for 40 min. The reaction was diluted with methylene chloride, sodium bicarbonate (5%) was added, and the phases were separated. The methylene chloride was evaporated to give the title compound, which was used directly in the following step: $[\alpha]^{25}_D$ −79.9° (ethanol, *c* = 1); TLC R_f = 0.19 (20% EtOAc/hexane); ^{1}H NMR δ 0.96−1.01 (t, 3 H), 1.88−2.17 (m, 2 H), 2.89 (s, 3 H), 5.54−5.59 (t, 1 H), 7.57−7.62 (t, 1 H), 7.70−7.73 (d, 1 H), 8.20−8.24 (m, 2 H).

(*R*)-Diethyl 1-[1-(3-Nitrophenyl)propyl]malonate (15). A solution of sodium ethoxide (1.0 M) was prepared by dissolving sodium metal (1.27 g, 0.055 mol) in absolute ethanol (55 mL). Diethyl malonate (8.84 g, 0.055 mol) was added to

the above solution at 0 °C. (*S*)-1-(3-Nitrophenyl)propanol mesylate (1.43 g, 5.5 mmol) was added dropwise to the above solution of sodium malonate (6.4 mL, 6.4 mmol) at −20 °C. After 2 h at 20−25 °C, an additional aliquot of sodium malonate (5 mL, 5.0 mmol) was added to the reaction and then stirred overnight at 20−25 °C. The reaction was concentrated and partitioned between ethyl acetate and hydrochloric acid (1 N). The organic phase was separated and the solvent removed to give crude product that was chromatographed (silica gel; ethyl acetate/hexane, 10/90) to give the title compound: $[\alpha]^{25}_D$ +19.4° (EtOH, $c = 1$); TLC $R_f = 0.48$ (20% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, TMS) δ 0.70−0.75 (t, 3 H), 0.96−1.00 (t, 3 H), 1.27−1.32 (t, 3 H), 1.56−1.88 (m, 2 H), 3.37−3.45 (d of t, 1 H), 3.65−3.69 (d, 1 H), 3.86−3.96 (m, 2 H), 4.21−4.28 (q, 2 H), 7.44−7.49 (m, 1 H), 7.54−7.57 (m, 1 H), 8.08−8.11 (m, 2 H).

3-(3-Nitrophenyl)pentanoic Acid ((+)-11) and Its Cyclohexylamine Salt from Malonate 15. [1-(3-Nitrophenyl)-propyl]malonate (+)-**15** (0.73 g, 2.26 mmol) was refluxed in 6 N HCl (10 mL) for 18 h. The reaction was cooled and extracted with EtOAc. The EtOAc layer was washed with water, separated, and evaporated to give 3-(3-nitrophenyl)pentanoic acid ((+)-**11**) (0.51 g) as a clear oil: $[\alpha]^{25}_D$ +13.3° (MeOH, $c = 1$); TLC $R_f = 0.48$ (2/20/80 AcOH/EtOAc/hexane); ^{1}H NMR δ 0.78−0.83 (t, 3 H), 1.59−1.82 (m, 2 H), 2.59−2.78 (d of q, 2 H), 3.07−3.17 (m, 1 H), 7.44−7.54 (m, 2 H), 8.04−8.10 (m, 2 H). 3-(3-Nitrophenyl)pentanoic acid ((+)-**11**) (0.3 g, 1.34 mmol) was dissolved in EtOAc (3 mL) and treated with cyclohexylamine (0.14 g, 1.41 mmol). The resulting crystals were filtered and rinsed with EtOAc to give 3-(3-nitrophenyl)pentanoic acid cyclohexylamine salt (0.306 g): mp 145−8 °C; $[\alpha]^{25}_D$ +11.8°; $[\alpha]^{25}_{578}$ +12.4° (MeOH, $c = 1.02$); IR (mull) 1636, 1550, 1348, cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_4 \cdot C_6H_{13}N$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.09; H, 7.88; N, 8.57.

(4-Phenylphenoxy)(4-chlorothiophenoxy)methane. To a slurry of paraformaldehyde (36.24 g, 1.21 mol, 1.58 equiv) in toluene (243 mL) at 22 °C was added aqueous hydrobromic acid (48.5 wt %, 652 mL, 5.86 mol, 7.68 equiv) with an endotherm to 18 °C. The resultant biphasic solution was warmed to 40 °C, and a solution of 4-chlorothiophenol (138.81 g, 0.960 mol, 1.26 equiv) in toluene (116 mL) was added over 0.5 h while the temperature was maintained at 40−43 °C and rinsed in with toluene (50 mL). The mixture was then warmed to 50 °C and stirred for 1 h. The mixture was cooled to 10 °C, the phases were separated, and the aqueous layer was washed with toluene (250 mL) The combined organics were treated with ice−water (500 mL) and hexanes (350 mL), and the phases were separated. The aqueous was then washed with toluene (200 mL), and the combined organics were dried on $MgSO_4$ and concentrated to give the crude bromomethyl thioether (268.01 g): ^{1}H NMR δ 7.43 (d, 2H, $J = 8.4$ Hz), 7.34 (d, 2H, $J = 8.7$ Hz), 4.79 (s, 2H); ^{13}C NMR δ 134.4 (s), 132.1 (d), 131.8 (s), 129.5 (d), 37.3 (t); HRMS (EI$^+$) calcd for C_7H_6-BrClS 235.9063, found 235.9063.

To a solution of 4-phenylphenol (129.91 g, 0.763 mol, 1.00 equiv) in DMF (400 mL) at −10 °C was added a solution of potassium *tert*-butoxide in THF (20 wt %, 429.40 g, 0.765 mol, 1.00 equiv) followed by THF (50 mL), while a temperature of <5 °C was maintained. The solution was concentrated to 557 g net weight and DMF (33 mL) added followed by the crude bromomethyl thioether prepared above with a free exotherm from 22 to 70 °C. The crude PNU-174652 was rinsed in with DMF (50 mL) and the resultant slurry stirred at 80 °C for 0.5 h. The mixture was cooled to 22 °C, and hexanes (400 mL) followed by water (500 mL) was added. The precipitate was collected by vacuum filtration, washed with water (1500 mL) and methanol (300 mL), and dried in a nitrogen stream to give a solid (251.25 g). This was dissolved in methylene chloride (1 L) and dried on $MgSO_4$, washing with methylene chloride (200 mL). A constant volume concentration (1300−1800 mL) was then performed while a total of 1.35 L methanol was added, and the final amount was 1344 g net weight. The resultant precipitate was collected at room temperature by vacuum filtration, washed with methanol (1 L), and dried at 65 °C under vacuum to give the mixed *S*,*O*-acetal (207.63 g, 83.2%): mp 99−101 °C; TLC $R_f = 0.64$ (10% EtOAc/hexanes); HPLC $t_R = 9.67$ min; ^{1}H NMR δ 7.55−6.99 (m, 13H), 5.44 (s, 2H); ^{13}C NMR δ 156.0 (s), 140.5 (s), 135.3 (s), 133.5 (s), 132.1 (d), 129.2 (d), 128.8 (d), 128.2 (d), 126.9 (d), 126.8 (d), 116.3 (d), 73.2 (t); MS (CI, NH_3) *m*/*z* (relative intensity) 328 (3.8), 326 (8.1), 200 (100). Anal. Calcd for $C_{19}H_{15}ClOS$: C, 69.82; H, 4.63. Found: C, 69.73; H, 4.59.

1-(Chloromethoxy)-4-phenylbenzene. To a solution of the mixed *S*,*O*-acetal prepared above (176.45 g, 539.9 mmol) in methylene chloride (750 mL) at 21 °C was added a solution of sulfuryl chloride (73.32 g, 543.2 mmol, 1.01 equiv) in methylene chloride (150 mL) while a temperature <23 °C was maintained over 8 min. The mixture was stirred at 20 °C for 11 min and then cooled to 3 °C. A solution of cyclohexene (60.7 mL, 599 mmol, 1.11 equiv) in methylene chloride (100 mL) was added over 10 min at 3−5 °C and then warmed to 19 °C and stirred 10 min. The solution was concentrated to 600 mL total volume, and hexanes (500 mL) was added. The solution was concentrated to 500 mL, and hexanes (300 mL) was added. The resultant slurry was concentrated to 500 mL and pentane (1.3 l) added. The slurry was cooled to −50 °C and the precipitate collected by vacuum filtration, washed with −30 °C pentane (700 mL), and dried to give a beige solid (115.28 g). A portion (110.34 g) was dissolved in methylene chloride (200 mL). Hexanes (1 L) was added and the mixture concentrated to 949 g. Hexanes (200 mL) was added and the mixture concentrated to 589 g. Hexanes (500 mL) was added, the slurry cooled to −30 °C, and the precipitate collected by vacuum filtration, washed with hexanes (300 mL), and dried to give the title compound (POMCl) as a gray solid (100.66 g, 89.0%): mp 67−70 °C; TLC $R_f = 0.68$ (8% EtOAc/hexanes); HPLC rt = 6.45 min; ^{1}H NMR δ 7.80−7.13 (m, 9H), 5.89 (s, 2H); ^{13}C NMR δ 155.0 (s), 140.3 (s), 136.5 (s), 128.8 (d), 128.4 (d), 127.1 (d), 126.9 (d), 116.4 (d), 77.2 (t); HRMS (EI$^+$) calcd for $C_{13}H_{11}ClO$ 218.0498, found 218.0493.

(*R*)-(4-Phenylphenoxy)methyl 3-(2-Phenylethyl)-3-[(4-phenylphenoxy)methoxy]hexanoate (17e). To a slurry of **6** (25.04 g, 64.62 mmol) in water (185 mL) and MTBE (185 mL) at room temperature was added aqueous hydrochloric acid (37.5 wt %, 7.51 g, 77.24 mmol, 1.20 equiv), and the pH was adjusted from 8.04 to 1.30. The phases were separated, and the aqueous phase was washed with MTBE (185 mL). The organics were dried on $MgSO_4$ and concentrated to an oil (18.39). To the oil were then added toluene (77 mL), *N*,*N*-diisopropylethylamine (96 mL, 551 mmol, 8.53 equiv), and PNU-174222E (71.88 g, 328.68 mmol, 5.09 equiv). The mixture was then warmed to 110 °C and stirred at 110−117 °C for 5 h. The mixture was cooled to 65 °C and methanol (800 mL) added. The resultant slurry was cooled to −30 °C and the product collected by vacuum filtration, washed with methanol (200 mL), and dried to afford crude **17e** (49.86 g, 56.5 wt % by HPLC, 72.6% yield). An analytical sample was obtained by chromatography (ethyl acetate/hexanes) followed by crystallization: mp 104.0−105.5 °C; TLC $R_f = 0.50$ (15% EtOAc/hexanes); HPLC $t_R = 13.8$ min; ^{1}H NMR δ 7.51−7.04 (m, 23 H), 5.78 (s, 2H), 5.32 (s, 2H), 2.75 (s, 2H), 2.64−2.58 (m, 2H), 2.03−1.97 (m, 2H), 1.78−1.72 (m, 2H), 1.41−1.28 (m, 2H), 0.86 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR δ 169.4 (s), 157.1 (s), 156.1 (s), 142.0 (s), 140.7 (s), 140.4 (s), 135.9 (s), 134.6 (s), 128.8 (d), 128.7 (d), 128.4 (d), 128.3 (d), 128.1 (d), 127.0 (d), 126.8 (d), 126.7 (d), 125.8 (d), 116.1 (d), 87.3 (t), 85.2 (t), 80.4 (s), 41.2 (t), 38.8 (t), 38.6 (t), 29.7 (t), 16.7 (t), 14.4 (q); MS (CI, NH_3) *m*/*z* (relative intensity) 618 (19), 266 (100); $[\alpha]^{25}_D$ −4 (C 1.0, CH_2Cl_2). Anal. Calcd for $C_{40}H_{40}O_5$: C, 79.97; H, 6.71. Found: C, 79.64; H, 6.58.

(*R*)-3-(2-Phenylethyl)-3-[(4-phenylphenoxy)methoxy]-hexanol (18e). To a slurry of crude **17e** (56.5 wt %, 49.32 g, 46.38 mmol) in toluene (500 mL) was added a solution of diisobutylaluminum hydride in toluene (1.52 M, 85 mL, 129.2 mmol, 2.79 equiv) while a temperature of −20 °C was maintained. The mixture was slowly warmed to 1 °C over 2.5 h and then stirred for 0.5 h. Acetone (8.0 mL, 108.5 mmol, 2.34 equiv) was added and the mixture cannulated into an 18 °C solution of citric acid monohydrate (136 g, 647.2 mmol, 14.0 equiv) in water (433 mL) with controlled exotherm to 28 °C,

rinsing with toluene (100 mL). The mixture was stirred at room temperature for 1.5 h, and the insolubles were removed by vacuum filtration, washing with toluene. The phases were separated in the filtrate, and the aqueous phase was washed with toluene (2 × 300 mL). The organics were dried on $MgSO_4$ and then washed with aqueous sodium hydroxide (0.5 M, 2 × 500 mL). The organics were concentrated to 137 g net weight, and methanol (250 mL) was added. The resultant slurry was concentrated to 212 g net weight, and methanol (250 mL) was added. The mixture was again concentrated to 253 g and methanol (250 mL) added. The slurry was cooled to −60 °C, and the insolubles were removed by filtration. The filtrate was concentrated 60 g net weight, hexanes (500 mL) added, and the mixture concentrated to 22 g net weight. Hexanes (500 mL) was added and the mixture again concentrated to 40 g net weight. Methylene chloride (25 mL) was added followed by a slow addition of hexanes (500 mL) and pentane (250 mL) with cooling to −55 °C. The product was collected by vacuum filtration, washed with pentane (200 mL), and dried in a nitrogen stream to give a white solid (16.03 g, 91.1 wt % PNU-174306 by HPLC, 77.8% yield). An analytical sample was obtained by chromatography (ethyl acetate/hexanes) followed by crystallization (methylene chloride/hexanes): mp 49−53 °C; TLC R_f = 0.14 (15% EtOAc/hexanes); HPLC t_R = 9.18 min; ^{1}H NMR δ 7.56−7.07 (m, 14H), 5.36 (s, 2H), 3.76−3.74 (m, 2H), 2.63−2.58 (m, 2H), 1.94−1.88 (m, 5H), 1.70−1.65 (m, 2H), 1.38−1.30 (m, 2H), 0.93 (t, 3H, J = 7.2); ^{13}C NMR δ 157.05 (s), 142.25 (s), 140.73 (s), 134.68 (s), 128.70 (d), 128.42 (d), 128.29 (d), 128.2 (d), 126.8 (d), 125.9 (d), 116.1 (d), 87.1 (t), 81.9 (s), 58.9 (t), 38.8 (t), 38.6 (t), 38.2 (t), 29.9 (t), 17.0 (t), 14.6 (q); MS (CI, NH_3) m/z (relative intensity) 422 (9.9), 252 (100); $[\alpha]^{25}_D$ +6 (C 1.0, CH_2Cl_2). Anal. Calcd for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.06; H, 7.86.

(*R*)-3-(2-Phenylethyl)-3-[(4-phenylphenoxy)methoxy]-hexanal (19e). To a solution of crude **18e** (91.1 wt %, 15.40 g, 34.68 mmol) in methylene chloride (47 mL) at 0 °C was added a solution of potassium bromide (0.4057 g, 3.409 mmol, 0.098 equiv) and sodium bicarbonate (1.557 g, 18.53 mmol, 0.53 equiv) in water (20.5 mL) followed by 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy, free radical (0.3060 g, 1.776 mmol, 0.051 equiv). Aqueous sodium hypochlorite (13.4 wt %/vol, 26.6 mL, 47.88 mmol, 1.38 equiv) was then added by syringe pump over 1 h while a temperature of 1−5 °C was maintained. A solution of sodium thiosulfate pentahydrate (0.5182 g, 2.088 mmol, 0.0602 equiv) in water (14 mL) was then added. The phases were separated at 0 °C, and the aqueous phase was washed with 2 × 50 mL of methylene chloride. The organics were immediately filtered through magnesol (50.25 g) and rinsed through with methylene chloride (400 mL). The extracts were concentrated to an oil (30 g), and hexanes (500 mL) was added. The mixture was concentrated to 250 g net weight, and hexanes (100 mL) was added. The mixture was concentrated to 186 g net weight, and pentane (300 mL) was added. The resultant slurry was cooled to −50 °C and the product collected by vacuum filtration, washed with −50 °C pentane (100 mL), and dried to give a white solid, analytically pure as PNU-174305 (13.77 g, 98.6%): mp 47.0−48.5 °C; TLC R_f = 0.41 (10% EtOAc/hexanes); HPLC t_R = 10.95 min; ^{1}H NMR δ 9.79 (t, 1H, J = 2.7 Hz), 7.53 (t, 4H, J = 7.5 Hz), 7.40 (t, 2H, J = 7.5 Hz), 7.26 (t, 2H, J = 8.1 Hz), 7.20−7.08 (m, 5H), 5.40 (s, 2H), 2.67 (t, 2H, J = 2.1 Hz), 2.65−2.56 (m, 2H), 1.99 (t, 2H, J = 8.4 Hz), 1.76 (t, 2H, J = 8.7 Hz), 1.38 (bq, 2H, J = 6.6 Hz), 0.93 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 201.8 (d), 156.9 (s), 141.7 (s), 140.7 (s), 134.8 (s), 128.7 (d), 128.5 (d), 128.3 (d), 128.2 (d), 126.8 (d), 126.0 (d), 116.0 (d), 87.2 (t), 80.4 (s), 50.1 (t), 39.2 (t), 39.1 (t), 29.7 (t), 16.9 (t), 14.5 (q); MS (CI, NH_3) m/z (relative intensity) 420 (3.5), 220 (100); $[\alpha]^{25}_D$ +14 (c 1.0, CH_2Cl_2). Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51; N, 0.00. Found: C, 80.59; H, 7.69; N, 0.08.

(3*R*,7*R*)-4-Carbomethoxy-3-(3-nitrophenyl)-7-(2-phenylethyl)-7-[(4-phenylphenoxy)methoxy]decan-5-ol (Mixture of Diastereomers at C-4 and C-5) (PNU-174698 (20)). To a solution of (*R*)-**8** (3.78 g, 15.932 mmol) in THF (55 mL) at −80 °C was added a solution of sodium hexamethyldisilazide in THF (0.935 M, 17.5 mL, 16.36 mmol, 1.027 equiv) over 7 min while a temperature of −80 to −85 °C was maintained. The resultant brown solution was then warmed to −74 °C and stirred at −74 to −76 °C for 18 min. The mixture was cooled to −90 °C, a solution of **19e** (6.50 g, 16.147 mmol, 1.013 equiv) in THF was added over 10 min while a temperature of −85 to −90 °C was maintained and rinsed in with THF (20 mL). The mixture was then warmed to −71 °C and saturated aqueous ammonium chloride solution (90 mL) added, followed by water (90 mL) and MTBE (90 mL), and the mixture warmed to room temperature. The phases were separated, and the aqueous phase was washed with MTBE (90 mL). The extracts were dried on $MgSO_4$ and concentrated to an oil (11.57 g, 79.0 wt % PNU-174698 by HPLC, 89.7% yield). An analytical sample was obtained by chromatography (ethyl acetate/hexanes): TLC R_f = 0.16, 0.24 (10% EtOAc/hexanes); HPLC t_R = 12.52, 12.68, 12.97 min; MS (electrospray, NaOAc) m/z (relative intensity) 662.5 (100). Anal. Calcd for $C_{39}H_{45}NO_7$: C, 73.21; H, 7.09; N, 2.19. Found: C, 73.22; H, 7.47; N, 1.99.

(3*R*,7*R*)-4-Carbomethoxy-3-(3-nitrophenyl)-7-(2-phenylethyl)-7-[(4-phenylphenoxy)methoxy]decan-5-one (Mixture of Diastereomers at C-4) (21). A solution of **20** (11.12 g, 79.0 wt %, 13.73 mmol) in methylene chloride (530 mL) was added to a ground mixture of pyridinium chlorochromate (16.099 g, 74.685 mmol, 5.44 equiv), sodium acetate (6.984 g, 85.14 mmol, 6.20 equiv), and Florisil (5.181 g) while a temperature of <11 °C was maintained. The mixture was warmed to 21 °C and stirred at room temperature for 20 h. The resultant brown slurry was filtered through magnesol (47.7 g) and rinsed with methylene chloride (375 mL). The filtrate was concentrated to an oil (10.38 g, 83.7 wt % PNU-174699 by HPLC, 99.2% yield). An analytical sample was obtained by chromatography (ethyl acetate/hexanes): TLC R_f = 0.34 (10% EtOAc/hexanes); HPLC t_R = 13.02,13.23 min; ^{1}H NMR δ 8.05−8.01 (m, 3H), 7.60−7.00 (m, 15H), 5.37 (s, 2H), 5.21 (q, 2H, J = 6.0 Hz), 4.03 (d, 1H, J = 10.8 Hz), 3.94 (d, 1H, J = 10.8 Hz), 3.75 (s, 1.5 H), 3.58−3.43 (m, 1H), 3.39 (s, 1.5H), 2.96 (d, 2H, J = 3.9 Hz), 2.78−1.37 (m, 7H), 1.20 (t, 1.5H, J = 7.2 Hz), 0.91 (t, 1.5H, J = 7.5 Hz), 0.71−0.61 (m, 3H); ^{13}C NMR δ 200.9 (s), 200.6 (s), 168.3 (s), 167.8 (s), 157.1 (s), 157.1 (s), 148.4 (s), 148.3 (s), 143.6 (s), 143.3 (s), 142.0 (s), 141.9 (s), 140.7 (s), 140.7 (s), 135.3 (d), 135.0 (d), 134.8 (s), 129.4 (d), 129.2 (d), 128.8 (d), 128.5 (d), 128.4 (d), 128.2 (d), 126.8 (d), 125.9 (d), 125.8 (d), 123.0 (d), 122.8 (d), 122.04 (d), 122.0 (d), 116.2 (d), 87.1 (t), 86.9 (t), 80.9 (s), 80.4 (s), 66.3 (d), 65.9 (d), 52.8 (q), 52.4 (q), 49.0 (t), 48.6 (t), 46.3 (d), 46.2 (d), 38.7 (t), 38.5 (t), 38.4 (t), 38.0 (t), 30.1 (t), 29.5 (t), 26.9 (t), 26.7 (t), 16.6 (t), 16.4 (t), 14.4 (q), 14.2 (q), 11.8 (q), 11.6 (q); MS (CI, NH_3) m/z (relative intensity) 656 (2.8), 655 (6.1), 136 (100). Anal. Calcd for $C_{29}H_{43}NO_7$: C, 73.45; H, 6.80; N, 2.20. Found: C, 73.11; H, 6.61; N, 2.26.

(3*R*,7*R*)-4-Carbomethoxy-7-hydroxy-3-(3-nitrophenyl)-7-(2-phenylethyl)decan-5-one (Mixture of Diastereomers at C-4) (22). To a solution of **21** (9.14 g, 83.7 wt %, 11.995 mmol) in THF (20 mL) at 23 °C was added a solution of sulfuric acid in methanol (0.524 M, 20 mL, 10.48 mmol, 0.87 equiv). The solution was allowed to stand at 23 °C for 22 h, and then a solution of sodium bicarbonate (3.52 g, 41.90 mmol, 3.49 equiv) in water (50 mL) was added, followed by MTBE (50 mL). The phases were separated, and the aqueous phase was washed with MTBE (30 mL). The combined organics were washed with aqueous sodium hydroxide (0.5 M, 2 × 50 mL) at 5 °C and then water (2 × 10 mL), then twice with a mixture of saturated aqueous ammonium chloride (15 mL) and water (35 mL). The organics were dried on magnesium sulfate and concentrated to an oil (6.29 g, 73.3 wt % PNU-173900 by HPLC, 84.4%). An analytical sample was obtained by chromatography (ethyl acetate/hexanes): TLC R_f = 0.39 (25% EtOAc/hexanes); HPLC t_R = 8.15, 8.50 min; ^{1}H NMR δ 8.15−7.85 (m, 3H), 7.48−7.01 (m, 6H), 3.99 (d, 1H, J = 11.1 Hz), 3.92 (d, 1H, J = 10.8 Hz), 3.78 (s, 1.5H), 3.50−3.39 (m, 5H), 3.38 (s, 1.5H), 3.32−1.21 (m, 8H), 0.95 (t, 1.5H, J = 7.1 Hz), 0.82 (t, 1.5H, J = 7.1 Hz), 0.74−0.67 (m, 3H); ^{13}C NMR δ 205.2 (s), 205.0 (s), 168.0 (s), 167.5 (s), 148.4 (s), 143.1 (s), 142.0 (s), 142.0 (s), 135.2 (d), 135.0 (d), 129.5 (d), 129.3 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 125.9 (d), 122.8 (d), 122.6 (d),

122.2 (d), 73.8 (s), 73.5 (s), 66.6 (d), 66.4 (d), 52.9 (q), 52.5 (q), 50.8 (t), 50.6 (t), 46.3 (d), 46.2 (d), 41.6 (t), 41.0 (t), 40.8 (t), 30.0 (t), 29.6 (t), 27.0 (t), 17.1 (t), 16.9 (t), 14.6 (q), 14.4 (q), 11.7 (q), 11.5 (q); MS (CI, NH_3) *m/z* (relative intensity 474 (2.1), 473 (7.8), 194 (100). Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.08. Found: C, 68.36; H, 7.31; N, 3.34.

[3α(*R*),6*R*]-5,6-Dihydro-4-hydroxy-3-[1-(3-nitrophenyl)-propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2*H*-pyran-2-one (23). A 4 °C solution of aqueous sodium hydroxide (1 M, 11.4 mL, 11.4 mmol, 1.89 equiv) in methanol (35 mL) was added to crude **22** (73.3 wt %, 3.740 g, 6.018 mmol) and rinsed in with methanol (45 mL) while a temperature of <5 °C was maintained. The mixture was vigorously stirred to dissolve the majority of the crude oil and then moderately stirred at 0−5 °C for 67 h. The mixture was cooled to −5 °C and hexanes (90 mL) added. The phases were separated at <5 °C, and the organic phase was washed at <5 °C with a mixture of methanol (50 mL) and water (7 mL). The pH of the combined aqueous was adjusted from 12.55 to 6.24 at <5 °C with acetic acid (1.52 g, 25.31 mmol, 4.21 equiv). The aqueous was concentrated, extracted with methylene chloride (2 × 40 mL), dried on $MgSO_4$, and concentrated to give a crude oil (3.98 g). To a sample of the crude oil (0.401 g) was added diethyl ether (1.0 mL). The resultant slurry was cooled to −30 °C and the precipitate collected by vacuum filtration, washed with cold diethyl ether, and dried in a nitrogen stream to give a white solid, analytically pure as **23** (0.176 g, 75.1%): TLC $R_f = 0.49$ (50% EtOAc/hexanes); HPLC $t_R = 6.93$ min; ^{1}H NMR (1:1 $CDCl_3/CD_3OD$) δ 8.08 (s, 1H), 7.80 (d, 1H, $J = 8.4$ Hz), 7.56 (d, 1H, $J = 7.8$ Hz), 7.22 (t, 1H, $J = 8.1$ Hz), 7.07−6.88 (m, 5H), 3.98 (dd, 1H, $J = 6.9$, 9.3 Hz), 3.33−3.30 (m, 1H), 2.50−2.37 (m, 4H), 1.92−1.70 (m, 3H), 1.58−1.50 (m, 2H), 1.22−1.14 (m, 2H), 0.76 (t, 3H, $J = 7.2$ Hz), 0.72 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (1:1 $CDCl_3/CD_3OD$) δ 169.1 (s), 166.7 (s), 148.7 (s), 147.8 (s), 142.0 (s), 135.3 (d), 129.2 (d), 129.0 (d), 128.7 (d), 126.6 (d), 123.5 (d), 121.2 (d), 105.1 (s), 81.4 (s), 42.6 (d), 40.4 (t), 40.1 (t), 36.8 (t), 30.4 (t), 25.0 (t), 17.4 (t), 14.5 (q), 13.0 (q); MS (CI, NH_3) *m/z* (relative intensity) 441 (100); $[\alpha]^{25}_D$ +48 (*c* 1.0, CH_3CN). Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.61; H, 6.91; N, 3.26.

[3α(*R*),6*R*]-3-[1-(3-Aminophenyl)propyl]-5,6-dihydro-4-hydroxy-6-[1-(2-phenyl)ethyl]-6-propyl-2*H*-pyran-2-one (24). To a solution of **23** (0.6993 g, 1.651 mmol) in THF (50 mL) was added 5% Pd/C (50% water wet, 0.2574 g, 0.06048 mmol, 0.0366 equiv) and the mixture hydrogenated at 50 psi on a Parr shaker for 21 h. Celite (2.07 g) was added and the catalyst removed by vacuum filtration and rinsed with THF. The filtrate was concentrated to a white foam (0.665 g, 102.3% crude yield): TLC $R_f = 0.45$ (50% EtOAc/hexanes); HPLC $t_R = 5.18$ min; ^{1}H NMR (CD_3OD) δ 7.25−7.07 (m, 5H), 6.95 (t, 1H, $J = 7.7$ Hz), 6.81−6.75 (m, 2H), 6.52 (bd, 1H, $J = 5.8$ Hz), 3.95 (dd, 1H, $J = 6.7$, 9.5 Hz), 2.65−2.21 (m, 4H), 2.20−2.03 (m, 1H), 2.02−1.65 (m, 5H), 1.40−1.33 (m, 3H), 0.89 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR (CD_3OD) δ 170.3 (s), 167.4 (s), 147.4 (s), 142.9 (s), 129.5 (d), 129.3 (d), 126.9 (d), 119.9 (d), 116.9 (d), 114.4 (d), 106.3 (s), 81.7 (s), 43.6 (d), 40.8 (t), 40.5 (t), 37.6 (t), 30.9 (t), 25.9 (t), 17.9 (t), 14.7 (q), 13.4 (q); MS (CI, NH_3) *m/z* (relative intensity) 411 (100), 394 (89); $[\alpha]^{25}_D$ +28 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.13; H, 7.90; N, 3.38.

5-(Trifluoromethyl)-2-pyridinesulfonyl Chloride. To a well-agitated slurry of 5-(trifluoromethyl)-2-pyridinethiol (50.00 g, 279.1 mmol) in aqueous hydrochloric acid (1 M, 750 mL, 750 mmol, 2.69 equiv) was sparged chlorine gas (60 g, 846 mmol, 3.0 equiv) while a temperature of 0−5 °C was maintained. Methylene chloride (363 mL) was added, and the phases were separated at 0 °C. The aqueous phase was washed with methylene chloride (181.5 mL), and the combined organics were washed with water (2 × 300 mL) at 0−5 °C. The organics were dried on Na_2SO_4, filtered, and rinsed through with methylene chloride (62 mL) at 0 °C. A sample of this solution (125 g) was washed with aqueous sodium metabisulfite (5 wt %/vol, 62.5 mL) and water (62.5 mL), dried over Na_2SO_4, filtered, and stored at −70 °C for use in the next step.

[*R*-(*R,*R**)]-*N*-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2*H*-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (1).** To a solution of crude **24** (0.555 g, 1.378 mmol) in methylene chloride (3.10 mL), DMSO (0.100 mL, 1.409 mmol, 1.02 equiv), and pyridine (0.56 mL, 6.92 mmol, 5.02 equiv) was added the crude solution of 5-(trifluoromethyl)-2-pyridinesulfonyl chloride in methylene chloride prepared above (5.23 mL, ∼2.3 mmol based on thiol, ∼1.7 equiv) at −25 to −30 °C over 2 h, titrating with the sulfonyl chloride solution to an HPLC endpoint of 1.4 area% residual **24**. Aqueous hydrochloric acid (1 M, 6.2 mL, 6.2 mmol, 4.50 equiv) and ethyl acetate (5.2 mL) were added and the phases separated. The aqueous was washed with methylene chloride (10 mL), and the combined organics were dried on magnesium sulfate and concentrated to an oil. This oil was loaded on a 9.76 g silica gel column packed with 10% ethyl acetate in hexanes and the product eluted with the following ethyl acetate in hexanes mixtures (50 mL 10%, 100 mL 20%, 100 mL 30%, and 50 mL 40%). The eluent was combined and concentrated to an oil with an ethyl acetate chase. Ethyl acetate (5.2 mL) was added and the product precipitated by slow addition of heptane (15 mL). The resultant slurry was cooled to −30 °C and the precipitate collected by vacuum filtration, washed with a −30 °C mixture of ethyl acetate (1 mL) and heptane (4 mL), and dried in a nitrogen stream to give a white solid (0.6431 g, 77.4%, 97.10 wt % PNU-140690): mp = 86−89 °C; TLC $R_f = 0.66$ (50% EtOAc/hexanes);^{1}H NMR (CD_3OD) δ 8.94 (s, 1H), 8.19 (d, 1H, $J = 8.3$ Hz), 8.02 (d, 1H, $J = 8.2$ Hz), 7.25−6.97 (m, 9H), 3.93 (t, 1H, $J = 9.0$ Hz), 2.68−2.52 (m, 4H), 2.15−2.09 (m, 1H), 1.96−1.64 (m, 4H), 1.33 (q, 2H, $J = 7.9$ Hz), 0.88 (t, 3H, $J = 7.1$ Hz), 0.83 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (CD_3OD) δ 169.9 (s), 167.0 (s), 161.6 (s), 148.1 (d), 147.6 (s), 142.8 (s), 137.7 (s), 137.0 (d), 130.1 (qs, $J = 33$ Hz), 129.5 (d), 129.3 (d), 127.0 (d), 126.1 (d), 124.2 (d), 122.6 (d), 120.3 (d), 106.2 (s), 81.9 (s), 43.6 (d), 40.5 (t), 40.5 (t), 37.4 (t), 30.9 (t), 25.8 (t), 17.9 (t), 14.7 (q), 13.3 (q); MS (CI, NH_3) *m/z* (relative intensity) 621 (1.7), 620 (5.4), 603 (3.4), 148 (100); IR (mull) 1596, 1359, 720 cm^{-1}. Anal. Calcd for $C_{31}H_{33}N_2O_5S$: C, 61.78; H, 5.52; N, 4.65. Found: C, 61.47; H, 5.56; N, 4.58.

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