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Development and Pilot-Scale Demonstration of a Process for Inhibitors of the HIV Nucleocapsid Protein, NCp7

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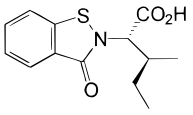
Abstract:

A manufacturing process to prepare two antiretroviral agents that denature the HIV-1 nucleocapsid protein (NCp7) has been developed and demonstrated on a pilot scale. 2,2′-Dithiobis-(benzoyl chloride) (4), prepared from commercially available 2,2′-dithiobis(benzoic acid) (3), was coupled directly with L-isoleucine to give the potential anti-HIV compound [*S*-(*R,*R**)]-2-{[2-[[2-[(1-carboxy-2-methylbutyl)carbamoyl]phenyl]dithio]-benzoyl]amino}-3-methylpentanoic acid (2) thereby eliminating the α-amino acid protection and deprotection steps used in the original synthesis. Compound 2 was oxidized by bromine to a second potential anti-HIV compound [*S*-(*R**,*R**)]-3-methyl-2-(3-oxo-3*H*-benzo[*d*]isothiazol-2-yl)pentanoic acid (1). The intermediacy of the hydrobromide salt of 1 provided an effective purity control in the production of the pharmaceutical agent. Cost, operational, safety, environmental, and equipment considerations were taken into account during the course of development.**

Introduction

The extremely rapid replication dynamics of the human immunodeficiency virus (HIV) has led to the continued search for new therapeutic agents directed at new viral targets. Together with reverse transcriptase and protease inhibitors, such agents could form part of the combination therapy currently used in the treatment of acquired immune deficiency syndrome (AIDS). Compounds **1** (CI-1012) and **2** (CI-1013) belong to a new class of antiretroviral agents that interfere with the HIV-1 nucleocapsid protein (NCp7), a highly conserved zinc-finger retroviral protein which mediates several essential steps of viral replication.[1] Both **1** and **2** affect the zinc-finger region of NCp7, causing rapid extrusion of zinc and subsequent denaturation of the viral protein.[2] **1** and **2** have been shown to inhibit HIV infection in vitro and are undergoing clinical investigation. In order to support clinical and toxicology studies, and the development of a dosage form, multi-kilogram quantities of both compounds were required. This necessitated the chemical development of efficient and economical processes to manufacture pharmaceutical quality **1** and **2** on a pilot scale of operation. Furthermore, the processes should be safe for routine operation, have minimum amounts of waste products associated with them, and preferably make use of standard production equipment. This paper describes the progress made towards achieving these goals.



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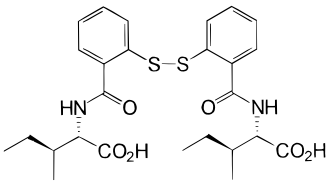

2

Results and Discussion

The obvious starting point for the development of manufacturing processes for **1** and **2** was the synthetic route used by the medicinal chemists to prepare the first gram quantities of each compound for in vitro testing. The route to **1** via **2** used one of the synthetic approaches previously employed to make benzoisothiazoles for investigation of their antibacterial and antifungal activity[3] and is shown in Scheme 1. Diacid chloride **4**, derived from 2,2′-dithiobis(benzoic acid) (**3**), was coupled with **6**, the *tert*-butyl ester derivative of L-isoleucine, to give **7**, the di-*tert*-butyl ester of **2**. Deprotection gave **2**, which in turn was oxidized to **1**. This synthesis had two attractive features from a development perspective. Firstly, the synthesis began with cheap, commercially available raw materials. 2,2′-Dithiobis(benzoic acid) is used widely in the photographic industry to stabilize photographic emulsions, and L-isoleucine (**5**) is a naturally occurring α-amino acid. Secondly, **1** was prepared from **2** by a linear sequence. This avoided the development of two separate syntheses, which was important since both compounds were being evaluated as drug candidates simultaneously. With this in consideration, the other common

(1) (a) Rice, G. R.; Supko, J. G.; Malspeis, L.; Buckheit, R. W.; Clanton, D.; Bu, M.; Graham, L.; Schaeffer, C. A.; Turpin, J. A.; Domagala, J.; Gogliotti, R.; Bader, J. P.; Halliday, S. M.; Coren, L.; Sowder, R. C.; Arthur, L. O.; Henderson, L. E. *Science* **1995**, *270*, 1194. (b) Domagala, J. M.; Bader, J. P.; Gogliotti, R. D.; Sanchez, J. P.; Stier, M. A.; Song, Y.; Vara Prasad, J. V. N.; Tummino, P. J.; Scholten, J.; Harvey, P.; Holler, T.; Grachek, S.; Hupe, D.; Rice, W. G.; Schultz, R. *Bioorg. Med. Chem.* **1997**, *5*, 569. (c) Gogliotti, R. D.; Elslager, E. F. U.S. Patent US 5,463,122, Dec 31, 1995. (d) Bolton, G. L.; Domagala, J. M.; Elslager, E. F.; Gogliotti, R. D.; Purchase, T. S.; Sanchez, J. P.; Trivedi, B. K. U.S. Patent US 5,620,997, April 15, 1997.

(2) Loo, J. A.; Holler, T. P.; Sanchez, J.; Gogliotti, R.; Maloney, L.; Reilly, M. D. *J. Med. Chem.* **1996**, *39*, 4313.

(3) (a) Gialdi, F.; Ponci, R.; Baruffini, A. *Farmaco, Ed. Sci.* **1961**, *16*, 509. (b) Davis, M. *Adv. Heterocycl. Chem.* **1972**, *14*, 43.

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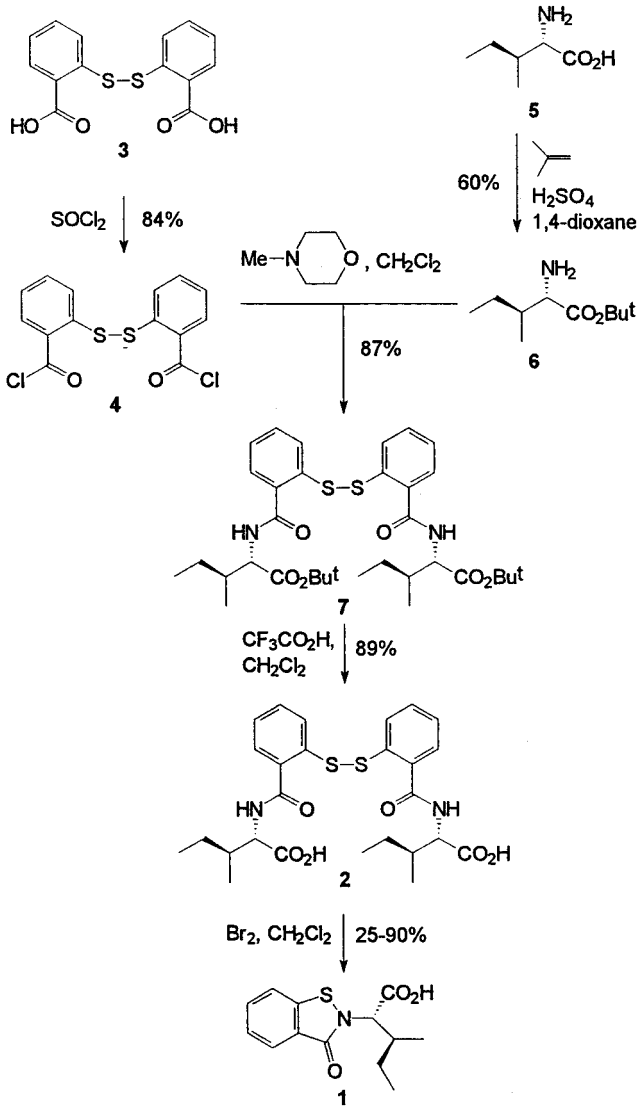
Scheme 1. **Discovery synthesis of 1 and 2**



method of preparing benzoisothiazoles, involving oxidation of **4** to *o*-chlorosulfenylbenzoyl chloride with chlorine followed by condensation with an amine, was not pursued.[4]

The synthetic process did, however, have a number of drawbacks from a manufacturing point of view. In the formation of **4**, thionyl chloride was used as both a reagent and a solvent, which would pose considerable safety and waste disposal concerns. The preparation of the *tert*-butyl ester of L-isoleucine by the isobutylene method[5] was particularly unattractive due to the use of 1,4-dioxane, a suspected cancer agent, as solvent and the use of large amounts of sulfuric acid, which would again present local waste disposal problems. Also, the work-up procedure was low throughput, consumed large volumes of diethyl ether, and ultimately gave only moderate yields of **6**. The elimination of methylene chloride as the solvent for the coupling, deprotection, and oxidation steps was highly

Scheme 2. **Process to prepare 2,2′-dithiobis(benzoyl chloride)**

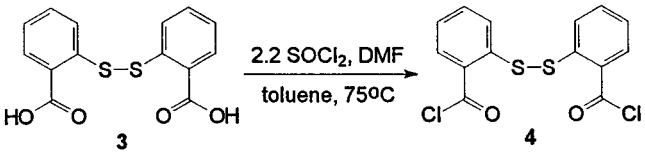


Table 1. **Pilot-scale preparation of 4**

pilot-plant campaign	amount of **4** produced (kg)	% yield of **4**
1	19	83
2	18	82
3	46	83

desirable. Methylene chloride is a suspected cancer agent and, being so volatile, is difficult to recover quantitatively. Lastly, the yield in the oxidation of **2** to **1** was widely variable, indicative of problems associated with the work-up and isolation of compound **1**. All of these issues had to be addressed during the course of development, which fell into three distinct areas: firstly, the development of a process for **4**; secondly, the development of a process to couple **4** with an L-isoleucine derivative; and thirdly, the development of a process for the oxidation of **2** to **1**. These areas are described in the following sections and include data from pilot-plant demonstrations of the processes.

Development of a Process for 2,2′-Dithiobis(benzoyl chloride) (4). A literature procedure was used as a basis for a pilot-scale process to convert **3** to **4**.[6] In the procedure, **3** was treated with thionyl chloride together with catalytic DMF in toluene (Scheme 2). A few minor modifications were made to the process, including an increase in the thionyl chloride charge to 2.2 equiv to increase the degree of conversion. Also, thionyl chloride was distilled out of the reaction mixture at atmospheric pressure and residual traces were displaced with additional toluene prior to crystallization. This allowed for safer isolation of the product and waste treatment of excess thionyl chloride in a separate reactor. Both modifications led to an approximately 12% increase in chemical yield. The process was successfully scaled up in three pilot-plant campaigns to produce 19−46 kg batches of **4** in consistent 82−83% yields from **3** (Table 1).

Development of a Process for [*S*-(*R,*R**)]-2-{[2-[[2-[(1-Carboxy-2-methylbutyl)carbamoyl]phenyl]dithio]-benzoyl]amino}-3-methylpentanoic Acid (2).** Process research began with the evaluation of a number of ester derivatives of L-isoleucine. The comparison was made on the basis of their accessibility, their coupling reactions with diacid chloride **4**, and deprotection of the precursors to **2**. The *tert*-butyl ester of L-isoleucine **6** used in the original synthesis was not commercially available and would, therefore, have to be prepared. The unattractiveness of this proposition has already been mentioned. Other methods for making this

(4) (a) Bordi, F.; Catellani, P. L.; Morini, G.; Plazzi, P. V.; Silva, C. *Farmaco, Ed. Sci.* **1989**, *44*, 795. (b) Grivas, J. C. *J. Org. Chem.* **1976**, *41*, 1325. (c) Allen, C. F. H.; Sagura, J. J. U.S. Patent US 2,870,015, Jan 20, 1959.

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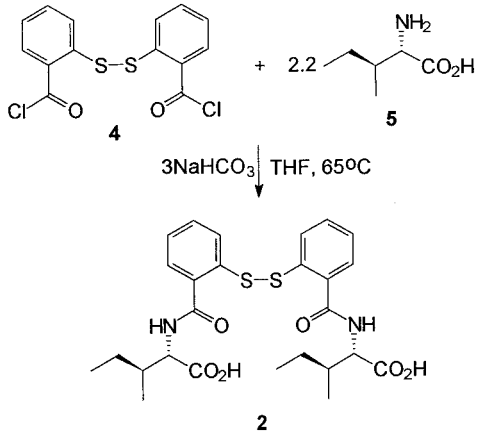
compound using *tert*-butyl acetate and perchloric acid[7] and *tert*-butyl iodide[8] have been described previously; however, each method has its own particular drawbacks in terms of practicality on an industrial scale.

The hydrochloride salt of L-isoleucine methyl ester and the *p*-toluenesulfonate salts of the benzyl and allyl esters of L-isoleucine were commercially available, although expensive. Each was coupled with **4** under conditions similar to those used for the *tert*-butyl ester, including the addition of an extra equivalent of *N*-methylmorpholine to neutralize the salt, to give good 80−90% yields of the coupled products. Deriving conditions for the deprotection of these products to **2** proved problematical. The dimethyl ester of **2** could not be deprotected under basic conditions due to the base sensitivity of the disulfide linkage. Aqueous acidic conditions gave only moderate conversions to **2**, which was also contaminated with a number of impurities that were not readily removed by recrystallization. Removal of the benzyl groups from the dibenzyl ester of **2** was not observed to any degree under a variety of catalytic hydrogenation conditions. Similarly, deprotection of the diallyl ester by Pd(0) catalysts was unsuccessful. These latter results are presumably due to the metal-poisoning effect of the disulfide group.

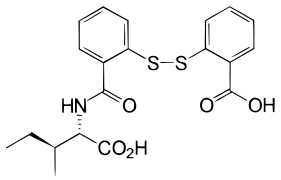
The problems associated with the preparation or sourcing of the L-isoleucine ester derivatives, as well as the difficulties encountered with the deprotection step, led us to investigate the coupling reaction between **4** and L-isoleucine itself to give **2** directly. A literature precedent did exist for this type of reaction in which **4** was coupled with L-glycine in 1,4-dioxane.[9] Under similar conditions, L-isoleucine gave **2** in an approximately 80% crude yield. The product could not, however, be purified sufficiently by recrystallization to give **2** that met specifications for pharmaceutical use. Furthermore, 1,4-dioxane is not a desirable solvent for use on a production scale. Other ether-type solvents were evaluated, and both methyl *tert*-butyl ether (MTBE) and di-*n*-butyl ether worked to a limited extent. THF, however, was found to give by far the best results in terms of product yield and purity and is also a common manufacturing solvent. Although L-isoleucine has only limited solubility in THF, even at reflux temperature, it was sufficient to give the desired product after a 10−12-h time period. Subsequently, it was found that the reaction was accelerated by the addition of an inorganic base, which happened to lead to further yield and purity improvements. In this regard, sodium bicarbonate (3 equiv) proved to be superior to both sodium and potassium carbonates (Scheme 3). The product **2** was extracted into MTBE and washed a number of times with water to remove excess L-isoleucine. It was noted during the work-up that the time for the MTBE and aqueous phases to separate became longer with each successive extraction, with the fourth extraction requiring several hours. This problem, which would have led to greatly increased cycle times on a pilot scale, was solved by adding dilute hydrochloric acid

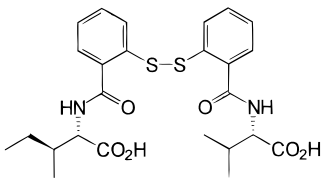
Scheme 3. **Process to prepare 2**



to the last two extractions. When the aqueous phase was kept acidic, the two layers separated almost instantaneously. Crude **2** was precipitated by the addition of hexane. If this material was to be used as an intermediate for conversion to **1**, no further purification was required. Pharmaceutical quality **2** was prepared after recrystallization from THF/hexane.

Under the conditions used to prepare **2**, no detectable epimerization at the α-amino acid center was found to occur. This is an additional benefit of using L-isoleucine in the process rather than an ester derivative. The only significant impurities detected in **2** were the half acid compound **8** and the half L-valine analog **9**. The former compound results from incomplete conversion in the coupling reaction, while the latter compound arises from the presence of trace amounts of L-valine in commercial L-isoleucine.





Following laboratory development, the process was successfully demonstrated on a pilot scale, and the results are summarized in Table 2. The process was used to prepare up to 54 kg of **2** in 73−75% yields after recrystallization, and the products from each campaign met specifications for pharmaceutical use. In order to further streamline the process for preparing **2** from 2,2′-dithiobis(benzoic acid), toluene-wet 2,2′-dithiobis(benzoyl chloride) may be used directly in the reaction with L-isoleucine. The 4−5% residual toluene on **4** is removed during subsequent processing. This has the advantage of eliminating a time-consuming drying step and enables the steps that produce **4** and **2** to be combined into a single uninterrupted process.

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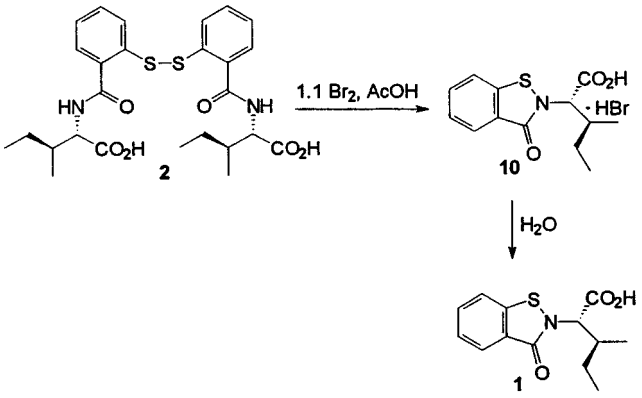
Table 2. **Pilot-scale preparation of 2**

pilot-plant campaign	amount of **2** produced (kg)		% yield of **2**	area % HPLC assay of **2**
	crude	recrystd		
1	13	12	74	99.7
2	10	9	73	99.7
3	60	54	75	98.7

Scheme 4. **Oxidation of 2 to 1**



Development of a Process for [*S*-(*R,*R**)]-3-Methyl-2-(3-oxo-3*H*-benzo[*d*]isothiazol-2-yl)pentanoic Acid (1).** The first change made to the original bromine oxidation process for the preparation of **1** from **2** was the replacement of methylene chloride with acetic acid, a more suitable solvent for use on a large scale. This modification produced an unexpected result, in that it led to the crystallization of a yellow solid from the reaction mixture. The solid was isolated and characterized as the hydrobromide salt, **10**, of compound **1** (Scheme 4). The identification of **10** was confirmed by the preparation of an authentic sample, obtained by treating an acetic acid solution of **1** with hydrogen bromide. IR spectroscopy suggested that the lactam carbonyl oxygen was protonated in the hydrobromide salt. The IR spectrum of **1** itself, taken as a 1% KBr disk, contained two strong carbonyl absorptions, one at 1735 cm^{-1} due to the carboxylic acid group and one at 1614 cm^{-1} due to the lactam. The IR spectrum of **10** still contained a strong absorption at 1747 cm^{-1}; however, the absorption due to the lactam carbonyl was greatly diminished in intensity. Surprisingly, a comparison of both the ^{1}H and ^{13}C NMR spectra of **1** and **10** in DMSO-d_6 showed very little difference between the two compounds, suggesting a rapid equilibrium between **1** and **10** in solution. The hydrobromide salt was stable in polar aprotic solvents like DMSO and acetonitrile; however, it was readily decomposed by protic solvents like water and alcohols, as evidenced by the immediate discharging of the yellow color upon exposure to these solvents.

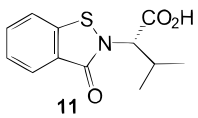
The formation and crystallization of **10** from acetic acid was also a fortuitous result in that it provided a very effective purification procedure for the production of the final pharmaceutical compound. The process was found to be very tolerant of the quality of **2** used in the oxidation, and it invariably gave **1** meeting purity specifications. The process to prepare **10** was simplified by elimination of the drying step. After filtration, **10** was washed with heptane, and the heptane-wet cake was used directly in the work-up procedure. An aqueous work-up was necessary to decompose **10** and to remove traces of residual acetic acid, MTBE being used as the solvent to extract the product **1**. The isolation of **1** from the organic solution proved to be the most challenging part of the process. In particular, the water content of the MTBE solution prior to crystallization was determined to be a critical process parameter. If the water content was above 0.7%, recoveries of **1** as a partial hydrate were good; however, when heat was applied during the drying process to remove residual solvents, the product melted to form an unworkable brick-like material. If the water content was below 0.4%, material recoveries were lower and the finer solid product was more difficult to filter off. The optimum range was found to be 0.4−0.7%, and this was achieved by a combination of a brine wash of the MTBE solution, an anhydrous magnesium sulfate treatment, and finally concentration of the solution. Due to the tendency for **1** to crystallize on the magnesium sulfate at ambient temperature, the treatment was performed at 45−50 °C. **1** was crystallized from the MTBE solution by the controlled addition of heptane.

Table 3. **Pilot-scale preparation of 1**

pilot-plant campaign	amount of **1** produced (kg)	% yield of **1**	w/w HPLC assay of **1**
1	7	74	99.5[a]
2	14	68	99.0
3	14	72	98.2
4	37	74	100

[a] Area % HPLC assay.

The process developed was successful in preparing **1** that met specifications for pharmaceutical use. The only impurities detected in the final product were unreacted starting material **2** and the L-valine analog **11** derived from compound **9**; these impurities fell within acceptable limits. Since **11**



had solubility characteristics similar to those of **1** and was not removed during crystallization, the levels of this impurity were controlled by placing specifications on L-valine in the L-isoleucine starting material. Again, no impurity arising from epimerization at the α-amino acid center was detected by chiral HPLC.

The process as described was transferred to the pilot plant and demonstrated up to a scale of 37 kg of **1**. These results are summarized in Table 3. Some aspects of the process did not perform as expected on the basis of previous laboratory experience. For example, reduction of the water levels in the MTBE solution was more difficult, and higher charges of heptane were required to initiate crystallization. Chemical yields were also approximately 5% lower than expected. The process did provide sufficient quantities of **1** to support the development of this promising anti-HIV candidate.

In summary, we have successfully developed and demonstrated a cost-effective, scalable synthetic process to manufacture both anti-HIV compounds **1** and **2**. Two chemical steps were eliminated from the original synthesis, and the process now employs reagents much more suitable for use on an industrial scale. The process does not require any specialized equipment, and we expect it to be scalable to produce even larger batch sizes of **1** and **2**.

Experimental Section

General Methods. All reagents, solvents, and processing aids are commercial products and were used as received. Pilot-scale reactions used glass-lined reactors having variable rate agitation, a −10 to 140 °C jacket temperature range, and a 60-mmHg vacuum to a 30-psig pressure rating. All equipment was inspected visually for cleanliness and integrity before use. Nitrogen was routinely used to break vacuums and to blanket reactions for safety reasons. Standard equipment-cleaning procedures were followed. An airline respirator, a rubber rain suit, rubber gloves, and rubber boots were worn by personnel during the charging of bromine and thionyl chloride, and local exhaust ventilation was used at the drum openings.

Melting points were measured on a Mettler FP80 apparatus and are uncorrected. Proton NMR spectra were recorded at 300.13 MHz and ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker AM300 spectrometer using tetramethylsilane as an internal standard. IR spectra were measured on Analect Diamond-20 and Bruker IFS 66 spectrometers, and the IR absorption bands reported have either strong or very strong intensities. Elemental analyses were performed on a CEC 440 elemental analyser. The following conditions were used for high-performance liquid chromatography (HPLC) analysis of **2**: Phenomenex Ultramex CN, 250 × 4.6 mm, 3-μm normal-phase column; 20% tetrahydrofuran in hexane with 0.1% trifluoroacetic acid mobile phase; 1.5 mL/min flow rate; 20-μL injection volume; detection at 251 nm. The following conditions were used for HPLC analysis of **1**: Alltech Hypersil BDS C18, 150 × 4.6 mm, 5-μm reverse-phase column; 680 mL of 0.5% aqueous triethylamine to pH 2.8 with phosphoric acid/320 mL of tetrahydrofuran; 1.2 mL/min flow rate; 20-μL injection volume; detection at 230 nm.

2,2′-Dithiobis(benzoyl chloride) (4). 2,2′-Dithiobis(benzoic acid) (50 kg, 163 mol), toluene (250 L), and *N*,*N*′-dimethylformamide (0.1 kg, 1.4 mol) were charged to a reactor. To the agitated mixture was added thionyl chloride (53.5 kg, 450 mol) followed by toluene (25 L) while the temperature was maintained below 35 °C. The mixture was heated at 70−75 °C for 16 h and filtered to remove suspended solids. The solids were washed with toluene (50 L), and the combined filtrates were heated to reflux. Thionyl chloride and toluene were distilled out of the mixture until a final batch volume of approximately 150 L remained in the reactor. Additional toluene (250 L) was added, and thionyl chloride and toluene were distilled out of the mixture under atmospheric conditions until a final batch volume of approximately 150 L remained. A further charge of toluene (250 L) was made and the batch volume reduced to approximately 150 L with a final batch temperature of 115 °C. The resulting solution was slowly cooled to 60−65 °C to give a slurry, which was further cooled to 0−5 °C. The slurry was filtered, and the filter cake was washed with toluene (200 L) and dried in a vacuum oven at 50−60 °C to give **4** (46.3 kg, 83%) as a tan-colored solid: mp 158.6−159.3 °C (lit.[6] mp 155−157 °C); IR (1% KBr disk) 1757, 1720, 1585, 1556, 1448, 1437, 1211, 1196, 877 cm^{-1}.

[*S*-(*R,*R**)]-2-{[2-[[2-[(1-Carboxy-2-methylbutyl)carbamoyl]phenyl]dithio]benzoyl]amino}-3-methylpentanoic Acid (2).** 2,2′-Dithiobis(benzoyl chloride) (46.2 kg, 135 mol), L-isoleucine (38.8 kg, 296 mol), sodium bicarbonate (34.2 kg, 407 mol), and THF (462 L) were charged to a reactor. With agitation, the mixture was heated to 60−65 °C and held at that temperature for 2 h. The reaction slurry was then added slowly to a rapidly stirred mixture of hydrochloric acid (37%, 37.6 kg), water (353 L), and MTBE (496 L) such that excessive foaming was avoided. The reactor was rinsed with THF (94 L), MTBE (95 L), and water (94 L), and the rinses were added to the quenched solution. The biphasic mixture was agitated rapidly for 15 min and allowed to settle. The lower aqueous phase was separated, and the upper organic layer was washed with water (235 L) followed by dilute hydrochloric acid (0.06%, 235 L, then 118 L). Hexane (663 L) was added to the MTBE/THF solution, and the resulting slurry was stirred at ambient temperature for 3 h and filtered. The filter cake was washed with hexane (120 L) and dried in a vacuum oven at 60−65 °C to give crude **2** (59.7 kg) as an off-white solid. The crude product and THF (1015 L) were charged to a reactor, and the mixture was heated to 60 °C to dissolve the solids. The solution was heated under reflux, and THF (730 L) was distilled out of the mixture. The solution was cooled to ambient temperature and filtered. The filtration equipment was rinsed with THF (25 L), and with rapid agitation, hexane (537 L) was added to the combined filtrates. The resulting slurry was stirred at ambient temperature for 17 h and filtered. The filter cake was washed with hexane (200 L), dried in a vacuum oven at 60−65 °C, and milled to give **2** (53.6 kg, 75%) as a white powder: mp 210.3−212.3 °C; $[\alpha]^{25}_{D}$ −31.4° (c = 1.00, MeOH); HPLC (w/w vs reference standard) 98.7%; ^{1}H NMR (DMSO-d_6) δ 12.7 (br s, 2H), 8.71 (d, J = 8.3 Hz, 2H), 7.67 (dd, J = 8.1, 1.1 Hz, 2H), 7.66 (dd, J = 7.4, 1.5 Hz, 2 H), 7.45 (ddd, J = 8.1, 7.4, 1.5 Hz, 2H), 7.31 (ddd, J = 7.4, 7.4, 1.1 Hz, 2H), 4.36 (dd, J = 8.3, 6.8 Hz, 2H), 1.96 (dddq, J = 8.7, 6.8, 6.8, 4.2 Hz, 2H), 1.53 (ddq, J = 13.6, 7.4, 4.2 Hz, 2H), 1.32 (ddq, J = 13.6, 8.7, 7.4 Hz, 2H), 0.97 (d, J = 6.8 Hz, 6H), 0.89 (t, J = 7.4 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 172.8, 167.2, 136.6, 133.8, 131.0, 128.4, 125.8, 125.8, 57.1, 35.8, 25.0, 15.6, 11.1; IR (Nujol) 3297, 2969, 2876, 1718, 1633, 1530 cm^{-1}. Anal. Calcd for $C_{26}H_{32}N_2O_6S_2$: C, 58.63; H, 6.06; N, 5.26. Found: C, 58.49; H, 6.06; N, 5.19.

[*S*-(*R,*R**)]-3-Methyl-2-(3-oxo-3*H*-benzo[*d*]isothiazol-2-yl)pentanoic Acid (1).** A reactor was charged with **2** (50.0 kg, 94 mol) and acetic acid (332 kg). Bromine (16.5 kg, 103 mol) was added to the agitated mixture while the batch temperature was maintained at 22−30 °C, and the resulting

slurry was stirred at 22−30 °C for 6 h. The slurry was filtered, and the filter cake was washed with acetic acid (24 kg) and heptane (71 kg) to give **10** (60.4 kg, 8.1% residual solvents). To a reactor were charged **10**, MTBE (198 kg), and water (140 L). The biphasic mixture was agitated rapidly for 15 min and allowed to settle. The lower aqueous phase was separated and extracted with MTBE (29 kg). The combined MTBE extracts were washed with a solution of sodium chloride (32 kg) in water (106 L), warmed to 45−50 °C, and dried with anhydrous magnesium sulfate (5.6 kg) at 45−50 °C for 2.5 h. The magnesium sulfate slurry was filtered, and the filtration equipment was rinsed with MTBE (29 kg). MTBE was distilled from the combined filtrates at atmospheric pressure and a batch temperature of 55−60 °C until a final batch volume of approximately 170 L remained in the reactor. The solution was cooled to 45−50 °C, and heptane (80 kg) was added. The resulting slurry was cooled to ambient temperature and then to 10−15 °C and filtered. The filter cake was washed with heptane (42 kg), dried in a vacuum oven at 45−50 °C, and milled to give **1** (36.9 kg, 74.1%) as white crystals: mp 120.8−121.9 °C; $[\alpha]^{25}_{D}$ −30.2° (c = 1.01, MeOH); HPLC (w/w vs reference standard) 100.0%; ^{1}H NMR (DMSO-d_6) δ 13.3 (br s, 1H), 7.98 (ddd, J = 8.1, 0.9, 0.7 Hz, 1H), 7.91 (ddd, J = 7.9, 1.3, 0.7 Hz, 1H), 7.71 (ddd, J = 8.1, 7.2, 1.3 Hz, 1H), 7.45 (ddd, J = 7.9, 7.2, 0.9 Hz, 1H), 4.99 (d, J = 9.4 Hz, 1H), 2.10 (dddq, J = 9.4, 9.4, 6.6, 3.5 Hz, 1H), 1.28 (ddq, J = 13.6, 7.4, 3.5 Hz, 1H), 1.10 (ddq, J = 13.6, 9.4, 7.4 Hz, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 170.9, 164.9, 141.3, 132.1, 125.8, 125.4, 123.1, 121.6, 59.8, 36.2, 24.7, 15.4, 10.4; IR (0.5% KBr disk) 2968, 2565, 1739, 1591, 1454, 1212, 1186, 747 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 59.03; H, 5.55; N, 5.07.

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