Diastereoselective Synthesis of the HIV Protease Inhibitor Darunavir and Related Derivatives via a Titanium Tetrachloride-Mediated Asymmetric Glycolate Aldol Addition Reaction

Jordan M. Witte
Illinois State University, jordanwitte@gmail.com

Emmanuel Ayim
Illinois State University

Christopher J. Sams
Illinois State University

Jasmine B. Service
Illinois State University

Caitlyn C. Kant
Illinois State University

See next page for additional authors

Follow this and additional works at: https://ir.library.illinoisstate.edu/fpchem

Part of the Chemistry Commons

Recommended Citation

This Article is brought to you for free and open access by the Chemistry at ISU ReD: Research and eData. It has been accepted for inclusion in Faculty Publications – Chemistry by an authorized administrator of ISU ReD: Research and eData. For more information, please contact ISUReD@ilstu.edu.
Diastereoselective Synthesis of the HIV Protease Inhibitor Darunavir and Related Derivatives via a Titanium Tetrachloride-Mediated Asymmetric Glycolate Aldol Addition Reaction

Jordan M. Witte, Emmanuel Ayim, Christopher J. Sams, Jasmine B. Service, Caitlyn C. Kant, Lillian Bambalas, Daniel Wright, Austin Carter, Kelly Moran, Isabella G. Rohrig, Gregory M. Ferrence, and Shawn R. Hitchcock*

ABSTRACT: Darunavir is a potent HIV protease inhibitor that has been established as an effective tool in the fight against the progression of HIV/AIDS in the global community. The successful application of this drug has spurred the development of derivatives wherein strategic regions (e.g., P1, P1’, P2, and P2’) of the darunavir framework have been structurally modified. An alternate route for the synthesis of darunavir and three related P1 and P1’ derivatives has been developed. This synthetic pathway involves the use of a Crimmins titanium tetrachloride-mediated oxazolidine-2-thione-guided asymmetric glycolate aldol addition reaction. The resultant aldol adduct introduces the P1 fragment of darunavir via an aldehyde. Transamination with a selected amine (isobutylamine or 2-ethyl-1-butylamine) to cleave the auxiliary yields an amide wherein the P1’ component is introduced. From this stage, the amide is reduced to the p-amino alcohol and the substrate is then bis-nosylated to introduce the requisite p-nitrobenzenesulfonylamide component and activate the secondary alcohol for nucleophilic substitution. Treatment with sodium azide yielded the desired azides, and the deprotection of the p-methoxyphenoxyl group is achieved with the use of ceric ammonium nitrate. Finally, hydrogenation to reduce both the aniline and azide functionalities with concurrent acylation yields darunavir and its derivatives.

INTRODUCTION

Darunavir (1) is a highly effective HIV protease inhibitor that is used in combination antiretroviral therapies (cART) along with other antiretroviral medicinal agents for suppressing viral replication and ultimately reducing the viral load in patients. This drug was initially approved by the FDA in 2006 and the European Directorate for the Quality of Medicines and Health Care (The European Pharmacopoeia) in 2007 and fully approved in 2008 due to its high efficacy in combating HIV infection. The successful application of darunavir in combination therapies has inspired the pursuit of improved derivatives with the potential for even greater potency. In this context, the seminal efforts of Ghosh and coworkers laid the foundation for structural aspects of darunavir and the domains where the structure could be modified. In 2023, Raines and coworkers modified the structure of darunavir by modifying the P2’ region with the use of a benzoborolone group (see 2a and 2b) and demonstrated the utility of installing such groups as pharmacophores. Schiffer, Ali, and coworkers modified the P2 domain by introducing a phenolic methylene diethylphosphonate group in conjunction with the introduction of modifications of the P1’ and P2’ domains to afford darunavir derivative 3. This modification resulted in sustained potency against highly resistant HIV-1 variants.

Reiser and coworkers changed the P2 domain of darunavir by the use of an ethereal bicyclic cyclopentyl system resulting in low nanomolar IC₅₀ values. Ghosh and coworkers have been leaders in this field with the development of a number of darunavir derivatives wherein the P2 domain has been changed to enhance drug efficacy. In this context, darunavir derivative 5 was designed with modifications to the P1, P2, and P2’ domains to enhance interactions with the active site of the HIV-1 protease. The combined modifications led to enzyme inhibition that was markedly potent and yielded more insight into the nature of the binding properties of a series of related derivatives with the protease.
The dominant synthetic pathway for the preparation of darunavir and many of its derivatives has involved the use of either $\beta$-epoxy azide $6$ or commercially available $\beta$-epoxy carbamates $7\alpha,\beta$ ($\alpha$: $R = -\text{Boc}$; $\beta$: $R = -\text{CBz}$). An alternate pathway to the chiral structural framework of darunavir, which was developed by Funicello and coworkers, involves the preparation of a suitable vinyl ester (9) obtained from a ligand-free Suzuki-Miyaura coupling reaction (Figure 2). The Sharpless asymmetric dihydroxylation reaction is then used to create the requisite chiral centers necessary for the synthesis of darunavir.

There was an interest in determining the potential of using an asymmetric glycolate aldol addition pathway to achieve the synthesis of darunavir. Retrosynthetically, it is proposed that darunavir may be derived from the known intermediate $\beta$-azido alcohol 12 (Scheme 1). This material, in turn, may be
RESULTS AND DISCUSSION

Oxazolidine-2-thione [(S)-16] was prepared in 77% yield using the method of Wu and workers\textsuperscript{16} and subsequently acylated with p-methoxyphenoxyacetic acid in the presence of EDC and DMAP in dichloromethane to yield the N-(p-methoxyphenoxyacetyl)oxazolidine-2-thione (S)-10 in 83% yield after recrystallization (Scheme 2). The reaction conditions for this process were optimized (slow addition of the carboxylic acid as the final reagent to the reaction mixture) to suppress the formation of the self-condensation byproduct that is proposed to arise from a putative Claisen condensation.\textsuperscript{17} The acylated thione (S)-11 was then reacted with one equivalent of titanium tetrachloride and two equivalents of EDC and DMAP in dichloromethane to yield the bis-acylated oxazolidine-2-thione (S,R)-10 in 86% yield, purified by recrystallization from ethyl acetate.

Oxazolidines [(S)-16] and [(R)-16] were synthesized from the sulfurous acid-induced reduction of benzamides [(S)-17] and [(R)-17], respectively. The benzamides [(S)-17] and [(R)-17] were then acylated with p-methoxyphenoxyacetic acid and (S)-phenylglycinol-derived oxazolidine-2-thione [(S)-10] in the presence of EDC and DMAP to yield [(S)-11] and [(R)-11], respectively. The [(S)-11] and [(R)-11] were then reacted with titanium tetrachloride to yield [(S,S,R)-10] and [(R,S,R)-10], respectively, in 86% and 87% yield, purified by recrystallization from ethyl acetate.

The synthesis of Darunavir proceeded as follows: the Crimmins glycolate aldol addition reaction with [(S)-phenylglycinol-derived oxazolidine-2-thione] was followed by hydrogenolysis to yield [(S)-11]. The [(S)-11] was then acylated with p-methoxyphenoxyacetic acid and (S)-phenylglycinol-derived oxazolidine-2-thione [(S)-10] in the presence of EDC and DMAP to yield [(S,S,R)-10] in 86% yield. The [(S,S,R)-10] was then reacted with titanium tetrachloride to yield [(S,S,R)-10] in 86% yield, purified by recrystallization from ethyl acetate.
equivalents of triethylamine in an asymmetric glycolate aldol addition reaction with phenylacetaldehyde to generate the Evans syn-adduct (S,S,R)-10 in 86% yield and ≥95% diastereomeric purity after flash chromatography on silica gel.

The synthesis of the aldol adduct (S,S,R)-10 was successful but required chromatographic purification. In order to optimize this process, an alternate route for obtaining the key aldol adduct side chain was considered. Thus, (R)-phenylglycinol [(R)-16] was cyclized using the Wu conditions to afford thione [(R)-17] in 78% yield after recrystallization. The thione was acylated as before with EDC and DMAP using the optimized conditions to yield [(R)-11] in 81% yield as a crystalline solid. This material was then reacted with two equivalents of titanium tetrachloride at −78 °C and enolized by the addition of two equivalents of triethylamine. Treatment of the titanium enolate with phenylacetaldehyde yielded the desired non-Evans syn-aldol adduct (R,S,R)-10 in 87% yield (crude d.r. = 15:1) after recrystallization. The stereochemistry of the adduct was confirmed by single-crystal X-ray crystallography with the presence of the sulfur atom allowing clear assignment of absolute stereochemistry from the observed anomalous dispersion effects.

With the synthesis of the key aldol reaction optimized, syn-aldol adduct (R,S,R)-10 was reacted with isobutylamine and imidazole to afford the transamidation product, β-hydroxyamide 15, in 82% after recrystallization (Scheme 3). In like fashion, 2-ethylbutylamine was employed in the transamidation process to yield amide 18 in 87% isolated yield. The introduction of this group introduces the 2-ethylbutylamine group as an eventual P1’ modification of darunavir. Subsequent reduction of amide 15 using the Meyers-Periasamy conditions (NaBH₄/I₂ in THF) yielded the β-aminoalcohol 14 in 89% yield after flash chromatography. Amide 18 was reduced using a commercially available borane-dimethylsulfide complex and yielded the β-amino alcohol 19 in 62% yield after chromatographic purification.

At this stage, β-amino alcohols 14 and 19 were treated with two equivalents of p-nitrobenzenesulfonyl chloride, triethylamine, and DMAP. It was anticipated that the bis-p-nosylation process would streamline the overall reaction. However, the reaction proved to have challenges, apparently due to the stereoelectronic factors governing the initial N-sulfonfyltion vs the O-sulfonfyltion. Ultimately, the reaction required 1.1 equivalents of catalytic DMAP to reach the complete formation of the bis-p-nosylation product. The target O-p-
nitrobenzenesulfonyl-N-p-nitrobenzenesulfonamides 13 and 20 were obtained in 52% and 56% yield, respectively, as crystalline solids after recrystallization. Treatment of sulfonamides 13 and 20 with sodium azide in DMSO afforded a near quantitative conversion to the corresponding azides 21 and 22 in 99% and 96% recovered yield, respectively. The azides were not purified as the analysis of the NMR spectra suggested that the reactions were clean transformations.

γ-Azidosulfonamides 21 and 22 were deprotected using ceric ammonium nitrate as a means of oxidatively removing the p-methoxyphenoxy group (Scheme 4). The isolated yield for the formation of β-azido alcohols 12 and 23 was 45% and 40%, respectively, after flash chromatography. Efforts to improve the reaction by adjusting the stoichiometry and changing the solvent and reaction temperature were not fruitful. The use of alternate deprotecting agent DDQ did not improve the yield of the reaction.

This process was followed by the hydrogenolysis of the β-azido alcohols 12 and 23 using hydrogen gas (balloon) to form β-amino alcohol 16 in situ. The intermediates 24 and 25 were not isolated but were reacted with the bis(tetrahydrofuranyl) N-hydroxysuccinimidyl carbonate (26) to afford the target darunavir (1) and the related N-2-ethylbutyl darunavir derivative (27) in 52% and 50%, respectively, for the one-pot, two-reaction pathway.

There was an interest in demonstrating that the overall synthetic pathway could be employed to create a P1 modification of the darunavir base structure (Scheme 5). In this regard, oxazolidine-2-thione (R)-11 was reacted with titanium tetrachloride and triethylamine to form the titanium enolate that was subsequently alkylated with isobutyraldehyde to yield the aldol adduct 28 in 74% isolated yield in greater than 95% d.e. This material was reacted with isopropylamine and imidazole in dichloromethane. The crude reaction mixture yielded the desired product in combination with byproducts.
that appeared to be ring-opening products. To circumvent this issue, an alternate approach was taken in which the acyl imidazole was formed in situ and then the isopropylamine was added. This process yielded the targeted N-isopropylamide in 96% yield after recrystallization. The amide was reduced using borane-dimethylsulfide in THF to afford β-amino alcohol in 82%. The β-amino alcohol was subsequently treated with an excess of p-nitrobenzenesulfonyl chloride and DMAP to afford the desired bis(p-nitrobenzenesulfonylated) adduct in 57% yield after chromatographic purification. This material was then reacted with sodium azide to yield the corresponding azide in high yield. Based on the quality of the crude 1H NMR spectrum of this material, it was moved forward to the process of deprotection via the use of ceric ammonium nitrate. As with the synthesis of darunavir and its N-2-ethylbutyl derivative, the ceric ammonium nitrate only proved to have limited efficiency in removing the p-methoxyphenoxy protecting group. The deprotection yielded β-azido alcohol in 45% yield after chromatographic purification. The synthesis of the P1-isopropyl derivative proved led to the pursuit of another P1-darunavir derivative based on the P1-adamantyl darunavir derivative prepared by Ghosh and coworkers (see Scheme 8 in ref 15). It was originally proposed that the introduction of a hydrophobic and sterically demanding adamantyl group might provide further understanding of the protease inhibitor (PI)–protein interaction. It is proposed here that a contracted and truncated variant of the adamantyl system would also be a useful tool in probing the PI–protein interaction. To this end, the P1-adamantyl system was envisioned to be truncated down to the P1-neopentyl system illustrated in Scheme 6.

The pursuit of 38 was initiated with the titanium-mediated asymmetric aldol reaction of (R)-11 with 3,3-dimethylbutyraldehyde (Scheme 7). The reaction proved to be incomplete, perhaps due to the steric demand of the neopentyl-type structure of the aldehyde. As a recourse, oxazolidine-2-thione (S)-11 was employed in the asymmetric aldol addition reaction to afford aldol adduct in 82% yield and greater than 95:5 d.r. This product was reacted with imidazole in the presence of dichloromethane, leading to the in situ formation of the acyl imidazole that was tentatively identified by ESI-HRMS. Treatment of 40 with isobutylamine yielded amide in 96% yield. As before, the amide was reduced to the corresponding β-amino alcohol using a borane-dimethylsulfide complex. This process afforded a 93% yield after chromatographic purification. An attempt was made at the bis(sulfonylation) of β-amino alcohol using two equivalents of the p-nitrobenzenesulfonyl chloride. Unfortunately, the product that was obtained in 50% yield was the monosulfonylated product. The failure of the product to undergo bis(sulfonylation) was attributed to the steric hindrance imparted by the proximal neopentyl fragment. Thus, sulfonamide was treated with an excess of p-nitrobenzenesulfonyl chloride to afford the desired bis(sulfonylated) product in 77% yield. The reaction of 44 with sodium azide in DMSO led to the isolation of the azido neopentyl darunavir intermediate. Deprotection of the p-methoxyphenoxy protecting group was accomplished by the use of a 4:1 acetonitrile/water solution of ceric ammonium nitrate. The product β-azido alcohol was obtained in a 45% yield. The synthesis of the Azido Neopentyl Darunavir Derivative

Scheme 7. Synthesis of the Azido Neopentyl Darunavir Derivative

The Journal of Organic Chemistry
pubs.acs.org/joc
Article
https://doi.org/10.1021/acs.joc.4c01057
J. Org. Chem. XXXX, XXX, XXX–XXX
yield after chromatographic purification. Hydrogenation of β-
azido alcohol 46 in the presence of Pd/C and carbonate 26
yielded neopentyl darunavir derivative 38 in 73% isolated yield
after chromatography.

In conclusion, we have described an alternate preparative
route to the HIV protease inhibitor darunavir using an
asymmetric glycolate aldol addition reaction to form the key
stereocenters. A strategy that involved the using enantiomeric
oxazolidine-2-thione auxiliaries with opposing sterechemical
outcomes in the asymmetric aldol addition reaction was
successfully employed. A convergent strategy of introducing
the key p-nitrobenzene sulfonamide and activating the chiral
alcohol in the form of p-nitrobenzene sulfonate in the same
chemical step was also employed. The overall synthesis of
darunavir proved to be successful via the aldol addition
pathway, but the potential for improving the current route
remains open.

Experimental Section

Safety Considerations. It is noted that the formation of
oxazolidine-2-thiones (R)-17 and (S)-17 involves an exothermic
reduction/oxidation transformation that employs 30% hydrogen
peroxide. It is recommended that a highly efficient water condenser
is used for this reaction. The use of reagents such as titanium
tetrachloride (1 M in CH₂Cl₂) and borane-dimethyl sulfide complex
should be handled with care using air-free techniques.

General Methods.26,29 Unless otherwise noted, all chemical
reagents and solvents were purchased and used without further
purification. All reactions were conducted under a nitrogen
atmosphere in glassware that was flame-dried. Unless otherwise
indicated, chemical reagents that served as starting materials, chemical
reactants, and solvents were used as received from commercial
vendors (e.g., MilliporeSigma, ThermoFisher Scientific, and Combi-
Blocks, Inc.) without further purification. All reactions were conducted under a nitrogen
atmosphere in glassware that was flame-dried. Unless otherwise
noted, all chemicals were used as received.

(4S)-4-Phenyl-1,3-oxazolidine-2-thione [(S)-17].28 To a flame-
dried, nitrogen-purged 5 L round-bottom flask fitted with a Claisen
adapter with a pressure-equalizing addition funnel and a tall
condenser equipped with a stir bar were added 1-phenylglycinol
(13.7 g, 100 mmol, purchased from Combi-Blocks, Inc.), ethanol
(100 mL), potassium carbonate (6.95 g, 50.0 mmol), and carbon
disulfide (12 mL). The reaction was heated to 50 °C using a heating
mantele controlled by a variable transformer, and a 30% (w/v) aqueous
solution of hydrogen peroxide (17.0 mL, 167 mmol) was added
dropwise. Upon complete addition of the hydrogen peroxide, the
reaction was stirred for 15 min. The reaction is highly exothermic
and must be carefully monitored during this time. It is important
that the condenser is efficient and the system is open to the air. The reaction
was cooled to ambient temperature and gravity-filtered into a 1 L flask
to remove any solid material. The reaction flask was washed with ethyl
acetate (3 × 30 mL), and the rinses were combined with the filtrate.
The reaction solvent was then removed by rotary evaporation.
The reaction was then reconstituted in ethyl acetate (200 mL). The organic
layer was then washed with an aqueous solution of 1 M HCl
(2 × 80 mL) and brine (80 mL). The organic layer was then dried
(MgSO₄) and filtered, and the solvents were removed by rotary
evaporation. The crude solid product was then recrystallized
with ethyl acetate and hexanes to afford the title compound as a light-
yellow crystalline solid (13.7 g, 77 mmol, 77% yield). Melting point:
121–123 °C. 33 (δ = 1.00, CH₂CH₃), 1H NMR (500 MHz,
CDCl₃): δ 7.71 (broad singlet, 1H), 7.46–7.32 (m, 5H), 5.12
(dd, J = 8.9, 7.0 Hz, 1H), 5.00 (apparent triplet, J = 8.9, 7.0 Hz, 1H) ppm.
13C NMR (125 MHz, CDCl₃): δ 189.7, 138.0, 129.2, 129.2, 126.3, 77.7, 60.2 ppm. This material was
identical to that described by Wu and coworkers.16

(4R)-4-Phenyl-1,3-oxazolidine-2-thione [(R)-17].28 1-Phenylglycinol
(41.2 g, 300 mmol, purchased from Combi-Blocks, Inc.) was
employed. The product was recrystallized and was recovered as a
light-yellow crystalline solid (41.9 g, 234 mmol, 78% yield). Melting
point: 121–123 °C. 33 (δ = 1.00, CH₂CH₃), 1H NMR (500 MHz,
CDCl₃): δ 7.51 (broad singlet, 1H), 7.45–7.30 (m, 5H), 5.11
(dd, J = 8.9, 6.9 Hz, 1H), 5.00 (apparent triplet, J = 9.2 Hz, 1H), 4.49
(dd, J = 8.9, 6.9 Hz, 1H) ppm. 13C NMR (125 MHz, CDCl₃): δ 189.7,
138.0, 129.2, 129.2, 126.3, 77.7, 60.2 ppm. This material was
identical to that described by Wu and coworkers.16

(4S)-3-[p-Methoxyphenoxy]acetyl]-4-phenyl-1,3-oxazolidine-2-
thonic [(S)-11].28 To a flame-dried, nitrogen-purged 1000 mL round-
bottom flask equipped with a stir bar were added oxazolidine-2-thione
[(S)-17] (11.1 g, 61.4 mmol), dichloromethane (200 mL), EDC
(12.9 g, 67.5 mmol), and DMAP (1.90 g, 15.4 mmol). Once these
reagents had been added, p-methoxyphenylacetic acid (11.2 g, 61.4
mmol) was added portion-wise. The reaction mixture was then stirred
overnight, and then, the contents of the round-bottom flask
were transferred into a separatory funnel. The reaction mixture was then
mixed with an aqueous solution of 1 M HCl (60 mL). The organic
layer was separated from the aqueous layer and then treated with
an aqueous solution of 1 M NaOH (2 × 60 mL). The organic layer
was separated and finally washed with brine (60 mL). The organic layer
was collected, dried (MgSO₄), and gravity-filtered. The solvent was
removed by rotary evaporation, and the crude product was
recrystallized from ethyl acetate and hexanes to afford compound (S)-11 as a white crystalline solid (17.5 g, 50.9 mmol, 83%). Mp: 108–109 °C. \( [\alpha]_D = +83.2 \) (c = 1.00, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.40–7.30 \) (m, 5H), 6.82–6.76 (m, 4H), 5.73 (dd, \( J = 9.0, 3.3 \) Hz, 1H), 5.57 (dd, \( J = 17.7, 1.1 \) Hz, 1H), 5.45 (dd, \( J = 17.7, 1.1 \) Hz, 1H), 4.90 (apparent triplet, \( J = 9.0, 1.1 \) Hz, 1H), 4.58 (dd, \( J = 9.0, 3.3 \) Hz, 1H), 3.74 (3H) ppm. \(^13\)C{\(^1\)H} NMR (100 MHz, CDCl\(_3\)): \( \delta 185.0, 168.9, 154.5, 151.8, 138.2, 129.3, 129.1, 126.3, 115.9, 114.7, 75.4, 70.2, 62.0, 55.7 \) ppm. IR (CHCl\(_3\)): 1724, 1211, 821, 780 cm\(^{-1}\). HRMS (ESI-TOF) m/z: [M + Na]\(^+\) Calcd for C\(_{32}\)H\(_{33}\)NaO\(_3\)S\(_3\) 666.0770; Found, 666.0777. The material has been previously prepared.\(^{18a}\)

\((4R)-3-(4P-Methoxyphenoxo)acetyl-4-phenyl-1,3-oxazolidine-2-thione (R)-11\).\(^{28}\) Using the above procedure, oxazolidine-2-thione \((R)-\) was employed as the substrate. The reaction mixture was stirred for an additional 4 h, after which time the color of the solution transitioned from an amber color to that of deep purple upon the addition of the triethylamine. This solution was then washed with brine (200 mL), and anhydrous dichloromethane (1 L) was added dropwise by syringe. The solution was stirred for an additional 4 h, after which time the dry ice bath was removed, and brine (200 mL) was added dropwise to quench the reaction. The reaction contents were then removed by rotary evaporation to yield the crude reaction product as a tan solid, which was then re-crystallized using ethyl acetate and hexanes to afford the product as a crystalline solid (27.8 g, 81.0 mmol, 87% yield). Mp: 184–185 °C. \([\alpha]_D = -105.8 \) (c = 1.10, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.38–7.17 \) (m, 11H), 6.86–6.60 (m, 4H), 5.70 (dd, \( J = 9.2, 5.9 \) Hz, 1H), 4.85 (apparent triplet, \( J = 9.2, 1.1 \) Hz, 1H), 4.55–4.51 (m, 1H), 4.48 (dd, \( J = 9.2, 5.9 \) Hz, 1H), 3.76 (3H) ppm. \(^13\)C{\(^1\)H} NMR (100 MHz, CDCl\(_3\)): \( \delta 185.4, 170.4, 154.7, 151.1, 137.3, 137.0, 129.7, 129.2, 129.1, 128.5, 126.7, 126.5, 116.3, 114.9, 77.5, 74.7, 73.2, 62.6, 55.7, 40.4 \) ppm. IR (CHCl\(_3\)): 3424, 1717, 1216, 757 cm\(^{-1}\). HRMS (ESI-TOF) m/z: [M + Na]\(^+\) Calcd for C\(_{28}\)H\(_{28}\)NaO\(_4\)S\(_3\) 846.1346; Found, 846.1349. Suitable crystals for single-crystal X-ray diffraction analyses were grown by vapor diffusion of pentane into a dichloromethane solution of \((R,S,R)-10\).\(^{28}\)

\((4R)-3-[2S,3'R']-3-hydroxy-2-(p-methoxyphenoxy)-4-phenylbutanoyl]-4-phenyl-1,3-oxazolidine-2-thione ([R,S,R]-10).\(^{28}\) To a flame-dried, nitrogen-purged 5 L round-bottom flask equipped with a large stir bar were added acylated thione \((R)-11 \) (10.0 g, 29.1 mmol) and anhydrous dichloromethane (1 L). The reaction vessel was chilled to −78 °C with a dry ice/ethanol bath, and titanium tetrachloride (1 M in CH\(_2\)Cl\(_2\), 64 mL, 64 mmol) was added dropwise by syringe. The solution was stirred for 30 min, at which point triethylamine (8.90 mL, 64 mmol) was added by syringe. The color of the solution transitioned from an amber color to that of deep purple upon the addition of the triethylamine. This solution was stirred for 60 min at −78 °C, and freshly distilled phenylacetaldehyde (7.2 mL, 64 mmol) was added to the reaction vessel by syringe. The reaction mixture was stirred for an additional 4 h, after which time the dry ice bath was removed, and brine (200 mL) was added dropwise to quench the reaction. The reaction contents were allowed to gradually warm up to room temperature with vigorous stirring, transferred to a separatory funnel, and then extracted twice with an aqueous solution of 1 M HCl (100 mL). The organic layer was separated from the aqueous layer and subsequently washed with brine (100 mL), dried (MgSO\(_4\)), and filtered. The solvent was then removed by rotary evaporation to yield the crude reaction product as a tan solid, which was then recrystallized using ethyl acetate and hexanes to afford the pure product as a white crystalline solid (11.73 g, 25.45 mmol, 87% yield). Mp: 184–185 °C. \([\alpha]_D = -105.8 \) (c = 1.10, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.38–7.17 \) (m, 11H), 6.86–6.60 (m, 4H), 5.70 (dd, \( J = 9.2, 5.9 \) Hz, 1H), 4.85 (apparent triplet, \( J = 9.2, 1.1 \) Hz, 1H), 4.55–4.51 (m, 1H), 4.48 (dd, \( J = 9.2, 5.9 \) Hz, 1H), 3.76 (3H) ppm. \(^13\)C{\(^1\)H} NMR (100 MHz, CDCl\(_3\)): \( \delta 185.4, 170.4, 154.7, 151.1, 137.3, 137.0, 129.7, 129.2, 129.1, 128.5, 126.7, 126.5, 116.3, 114.9, 77.5, 74.7, 73.2, 62.6, 55.7, 40.4 \) ppm. IR (CHCl\(_3\)): 3424, 1717, 1216, 757 cm\(^{-1}\). HRMS (ESI-TOF) m/z: [M + Na]\(^+\) Calcd for C\(_{28}\)H\(_{28}\)NaO\(_4\)S\(_3\) 846.1346; Found, 846.1349. Suitable crystals for single-crystal X-ray diffraction analyses were grown by vapor diffusion of pentane into a dichloromethane solution of \((R,S,R)-10\).\(^{28}\)
material for the following reaction. Mp: 102–103 °C. [α]D = –6.51 (c = 1.04, CHCl3).1 H NMR (500 MHz, CDCl3): δ 7.27–7.16 (m, 5H), 6.88 (d, J = 9.3 Hz, 2H), 6.84 (d, J = 9.3 Hz, 2H), 6.60 (broadened triplet, 1H), 4.49 (d, J = 3.0 Hz, 1H), 4.30 (broad singlet, 1H), 3.78 (s, 3H), 3.17–3.09 (m, 2H), 2.97 (dd, J = 13.8, 5.2 Hz, 1H), 2.90 (dd, J = 13.8, 8.4 Hz, 1H), 2.77 (d, J = 7.5 Hz, 1H), 1.80–1.70 (m, 1H), 0.86 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H) ppm.13C NMR (125 MHz, CDCl3): δ 170.3, 155.1, 153.1, 137.7, 129.4, 128.5, 126.6, 116.6, 115.0, 80.7, 73.0, 55.7, 46.4, 39.6, 28.5, 20.0, 19.9 ppm. IR (nujol): 3310, 1653, 1215 cm–1.

The reaction flask was completed over the course of 15 min. The reaction was transformed and was subsequently stirred for 16 h. At the end of the reaction, the reaction was heated to reflux 18 h using a heating mantle controlled by a variable transformer. The reaction mixture was stirred overnight, diluted with dichloromethane, washed with an aqueous solution of M NaOH (30 mL) and brine (30 mL), and dried over MgSO4 and the solvent was removed by rotary evaporation. The crude residue was purified by flash column chromatography (3% methanol in dichloromethane) to afford 1A (5.07 g, 13.1 mmol, 87% yield) as a colorless oil that was used in the next step without further purification.

To a flame-dried, nitrogen-purged, 1000 mL round-bottom flask fitted with a Claisen adapter equipped with a condenser and pressure-equalizing addition funnel were added β-hydroxyamide (15) (133 g, 37.1 mmol) and THF (180 mL). Sodium borohydride (3.37 g, 89.0 mmol) was added incrementally to the flask and stirring was initiated. A solution of iodine (10.4 g, 40.8 mmol) in THF (70 mL) was prepared and carefully added to the addition funnel, whereafter dropwise addition of this solution into the reaction flask was completed over the course of 15 min. The reaction was heated to reflux using a heating mantle controlled by a variable transformer and was subsequently stirred for 16 h. At the end of the reaction time, the reaction was cooled to 0 °C and quenched by the dropwise addition of methanol (50 mL) via the addition funnel. The mixture was concentrated under reduced pressure and then extracted with EtOAc (150 mL) and an aqueous solution of 1 M NaOH (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, and gravity-filtered. The solvent was then removed by rotary evaporation to afford the corresponding amino alcohol as a colorless oil that was used in the next step without further purification (11.4 g, 33.1 mmol, 89% yield). [α]D = 9.3 (c = 0.562, CHCl3).1 H NMR (500 MHz, CDCl3): δ 7.27–7.17 (m, 5H), 6.88 (d, J = 9.3 Hz, 2H), 6.83 (d, J = 9.3 Hz, 2H), 6.50 (m, 1H), 4.49 (d, J = 3.0 Hz, 1H), 4.31–4.27 (m, 1H), 3.77 (s, 3H), 3.25 (t, J = 6.3 Hz, 2H), 2.97 (dd, J = 13.8, 5.0 Hz, 1H), 2.90 (dd, J = 13.8, 8.7 Hz, 1H), 1.39–1.32 (m, 1H), 1.29–1.16 (m, 1H), 0.84 (t, J = 7.4 Hz, 7H), ppm.13C NMR (100 MHz, CDCl3): δ 170.3, 155.1, 151.3, 137.7, 129.4, 128.5, 126.6, 116.6, 115.0, 80.6, 73.0, 55.7, 41.5, 40.9, 39.5, 23.6, 10.9, 10.8 ppm. IR (CDCl3): 3421, 3355, 1655, 1506, 1223, 1037, 827 cm–1. HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for C33H27N4NaO6S 386.2326; Found, 386.2328.

(25R,3R)-2-Hydroxy-4-(isobutylamino)-3-(p-methoxyphenoxy)-1-phenylbutane (14)26 To a flame-dried, nitrogen-purged, 1000 mL round-bottom flask fitted with a Claisen adapter equipped with a condenser and pressure-equalizing addition funnel were added β-hydroxyamide (15) (133 g, 37.1 mmol) and THF (180 mL). Sodium borohydride (3.37 g, 89.0 mmol) was added incrementally to the flask and stirring was initiated. A solution of iodine (10.4 g, 40.8 mmol) in THF (70 mL) was prepared and carefully added to the addition funnel, whereafter dropwise addition of this solution into the reaction flask was completed over the course of 15 min. The reaction was heated to reflux using a heating mantle controlled by a variable transformer and was subsequently stirred for 16 h. At the end of the reaction time, the reaction was cooled to 0 °C and quenched by the dropwise addition of methanol (50 mL) via the addition funnel. The mixture was concentrated under reduced pressure and then extracted with EtOAc (150 mL) and an aqueous solution of 1 M NaOH (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, and gravity-filtered. The solvent was then removed by rotary evaporation to afford the corresponding amino alcohol as a colorless oil that was used in the next step without further purification (11.4 g, 33.1 mmol, 89% yield). [α]D = 9.3 (c = 0.562, CHCl3).1 H NMR (500 MHz, CDCl3): δ 7.27–7.16 (m, 5H), 6.88–6.82 (m, 4H), 4.19 (td, J = 7.0, 1.9 Hz, 1H), 4.08–4.06 (m, 1H), 3.78 (s, 3H), 3.27 (dd, J = 12.7, 4.3 Hz, 1H), 3.03–2.93 (m, 2H), 2.73 (dd, J = 12.7 Hz, 2.4 Hz, 1H), 2.42 (dd, J = 11.5, 6.5 Hz, 1H), 2.32 (dd, J = 11.5, 7.0 Hz, 1H), 1.73–1.65 (m, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H) ppm.13C NMR (100 MHz, CDCl3): δ 154.4, 151.7, 138.7, 129.5, 128.4, 126.2, 117.3, 114.9, 76.6, 75.9, 58.0, 55.7, 50.6, 39.8, 28.2, 20.6, 20.5 ppm. IR (CHCl3): 3168, 1218 cm–1. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C23H28NO3 344.2220; Found, 344.2220.
To a stirred solution of β-amino alcohol 19 (2.16 g, 5.80 mmol) dissolved in dichloromethane (19 mL) were added p-nitrobenzenesulfonyl chloride (3.22 g, 14.5 mmol) and DMAP (0.782 g, 6.40 mmol). Lastly, triethylamine (3.20 mL, 21.3 mmol) was then added dropwise to the reaction mixture via an addition funnel. The reaction mixture was stirred overnight at room temperature. After completion, the reaction mixture was diluted with dichloromethane and washed with aqueous solution of 1 M HCl (2 × 30 mL). The organic layer was washed with brine, dried over MgSO4, and concentrated under reduced pressure to afford a crude yellow viscous oil. The crude viscous oil was crystallized from diethyl ether and hexanes to yield 20 (3.72 g, 4.99 mmol, 86% yield) as yellow crystals. Mp: 152.3–153.6 °C. [1H NMR (500 MHz, CDCl3): δ 8.62 (d, J = 9.0 Hz, 2H), 7.99 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 9.0 Hz, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.96 (t, J = 7.8 Hz, 2H), 6.77 (d, J = 9.2 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 9.2 Hz, 2H), 4.82 (dq, J = 9.6, 4.1 Hz, 1H), 8.25 (dq, J = 10.8, 4.1 Hz, 1H), 3.83 (dd, J = 15.5, 1.2 Hz, 1H), 3.79 (s, 3H), 3.61 (dd, J = 13.6, 6.2 Hz, 1H), 3.40 (dd, J = 13.6, 8.5 Hz, 1H), 3.31 (dd, J = 13.6, 6.2 Hz, 1H), 3.05 (dd, J = 14.6, 2.2 Hz, 1H), 2.64 (dd, J = 14.6, 10.8 Hz, 1H), 1.77–1.70 (m, 2H), 1.48–1.27 (m, 4H), 0.91 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H) ppm. [13C{1H} NMR (100 MHz, CDCl3): δ 155.0, 152.3, 149.72, 149.70, 145.9, 140.5, 135.6, 129.0, 128.7, 128.6, 128.3, 126.9, 124.3, 124.0, 116.3, 114.9, 82.5, 75.4, 55.7, 52.4, 46.5, 37.9, 34.2, 22.9, 22.6, 10.6, 10.2 ppm. IR (CDCl3): 3108, 1531, 1506, 1350, 855 cm−1. HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for C29H24N6NaO8S 604.2200; Found, 604.2205. 

N-(2R,3S)-3-[Azido-2-(p-methoxyphenoxy)-4-phenylbutyl]-N-(2-isobutyl)-p-nitrobenzenesulfonamide (21).29 To a flame-dried, nitrogen-purged 100 mL round-bottom flask equipped with a stir bar was added azide 21 (1.89 g, 3.41 mmol). Acetonitrile (56 mL) and deionized water (14 mL) were added in a 4:1 ratio to achieve an overall concentration of 0.049 M. Ceric ammonium nitrate (7.48 g, 13.7 mmol) was added, and the reaction was allowed to stir for 90 min. The reaction was then diluted with brine (20 mL), and the solvent was then removed by rotary evaporation. The concentrate was diluted with diethyl ether (150 mL), transferred to a separatory funnel, and extracted with brine (2 × 20 mL). The organic layer was dried over MgSO4, gravity-filtered, and concentrated under reduced pressure. The resulting crude residue was purified over silica using a mobile phase gradient (95:S, 80:20, hexanes:EtOAc) to afford the target azido alcohol as a dark, viscous oil (0.683 g, 1.53 mmol, 45% yield). [α]D = −3.2 (c = 1.19, CHCl3). [1H NMR (500 MHz, CDCl3): δ 8.86 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H), 7.35–7.32 (m, 2H), 7.29–7.25 (m, 2H), 3.79–3.75 (m, 1H), 3.66–3.62 (m, 1H), 3.31 (dd, J = 15.2, 9.3 Hz, 3H).
Darunavir (1). To a nitrogen-purged 250 mL round-bottom flask equipped with a stir bar were added azido alcohol (12) (0.680 g, 1.52 mmol), methanol (15 mL), and activated palladium on carbon (70 mg, 10% w/w). The flask was equipped with a hydrogen balloon, and the system was stirred for 17 h. The mixture was then filtered through Celite with ethyl acetate, concentrated under reduced pressure, and reconstituted in THF (15 mL). Commercially available carbamate 19 (0.412 g, 1.53 mmol) and triethylamine (0.32 mL, 2.3 mmol) were added, and the system was stirred overnight. The reaction mixture was concentrated under reduced pressure and subsequently purified over silica using 50% EtOAc in dichloromethane as the eluent to yield darunavir (1) as an amorphous solid (0.43 g, 0.78 mmol, 52% yield). Mp: 74–75 °C. 

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl[(25,3R)-4-(4-amino-N-(2-ethylbutyl)phenyl sulfonamido)-3-hydroxy-1-phenyl-2-butyl]carbamate (27). A round-bottom flask containing 23 (0.356 g, 0.749 mmol), 5% palladium on carbon (0.004 g), 2,5-dioxopyrrolidin-1-yl[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl]-carbonyl (0.162 g, 0.598 mmol), and TMF (25 mL) was flushed with N2 gas for 10 min. A balloon filled with hydrogen gas was then connected to the reaction flask, and the mixture was allowed to stir overnight at ambient temperature. After completion, the reaction mixture was diluted with chloroform, filtered through a 1:1 mixture of Celite and MgSO4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (diethyl ether) to afford the protease inhibitor 27 (0.217 g, 0.350 mmol, 50% yield) as a pale-yellow viscous oil. [α]D = +2.6° (c = 1.00, CHCl3). 

HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for C29H31N9O4S Na2 548.2425; Found, 548.2418.

(4R)-3-[(2S',3R')-3-Hydroxy-2-(p-methoxyphenoxy)-4-methylpentanoyl]-1,3-oxazolidine-2-thione (28). A flame-dried 3 L round-bottom flask fitted with a Claisen adapter and an addition funnel was fitted onto the Claisen adapter was charged with (R)-11 (10.0 g, 29.1 mmol) and dichloromethane (1 L). The reaction mixture was cooled to –78 °C and titanium tetrachloride (1 M in dichloromethane, 32.0 mL, 23.2 mmol) was added via the addition funnel. The reaction mixture was stirred for 30 min, and then the mixture was cooled to –78 °C. The second batch of titanium tetrachloride (32 mL) was added as before. After another 30 min of stirring, the mixture was warmed to 10 °C and then quenched with hydrochloric acid (4 M). The reaction mixture was filtered through a 1:1 mixture of Celite and MgSO4, and concentrated under reduced pressure. The resulting crude viscous oil was crystallized from ethyl acetate and hexanes to yield darunavir (1) as an amorphous solid (0.43 g, 0.78 mmol, 52% yield). Mp: 74–75 °C. 

HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for C29H31N9O4S Na2 548.2425; Found, 548.2418.
afford compound 28 as a white crystalline solid (8.89 g, 21.5 mmol, 74% yield). Mp: 149.5–151.5 °C. 

**1** H NMR (500 MHz, CDCl₃): δ 7.39–7.29 (m, 5H), 7.02 (d, J = 1.8 Hz, 1H), 6.85–6.79 (m, 4H), 5.73 (dd, J = 9.3, 6.5 Hz, 1H), 4.88 (t, J = 9.3 Hz, 1H), 4.50 (dd, J = 9.3, 6.5 Hz, 1H), 3.93 (ddd, J = 10.2, 8.4, 1.8 Hz, 1H), 3.74 (s, 3H), 2.05–1.95 (m, 1H), 1.60 (d, J = 10.2 Hz, 1H), 1.06 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H) ppm. 

**13** C (¼ H) NMR (100 MHz, CDCl₃): δ 185.5, 171.1, 154.6, 151.2, 136.7, 129.2, 129.1, 126.6, 116.0, 114.8, 77.5, 76.7, 74.7, 62.8, 55.7, 32.4, 19.2, 19.1 ppm. IR (CDCl₃): 3454, 1727, 1228, 825 cm⁻¹. HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₂H₁₆Na₂O₃S: 416.1526; Found, 416.1523.

![Diagram](https://https://doi.org/10.1021/acs.joc.4c01057)

### (2R,3R)-3-Hydroxy-N-isobutyl-2-(p-methoxyphenoxo)-4-methyl-pentanamid (30)

To a stirring solution of aldol adduct 28 (5.36 g, 12.9 mmol) in dichloromethane (129 mL) was added imidazole (2.63 g, 38.6 mmol). After 1 h, isobutylamine (1.30 mL, 13.1 mmol) was added to the reaction mixture, and the reaction was stirred overnight. The reaction mixture was diluted with dichloromethane (30 mL) and washed twice with an aqueous solution of NaOH (2 × 40 mL). The organic layer was then washed with brine (40 mL), dried over MgSO₄ and concentrated under reduced pressure to afford compound 33a (3.80 g, 12.2 mmol, 95% yield) as pure white crystals. The crystals obtained were pure and did not require further purification. Mp: 84–86 °C. 

**1** H NMR (500 MHz, CDCl₃): δ 6.88 (d, J = 9.3 Hz, 2H), 6.83 (d, J = 9.3 Hz, 2H), 6.49 (broad triplet, 1H), 4.56 (d, J = 2.6 Hz, 1H), 4.30 (broad singlet, 1H), 3.77 (s, 3H), 3.73 (dd, J = 7.8, 1.6 Hz, 3H), 3.12 (t, J = 6.6 Hz, 2H), 2.01–1.92 (m, 1H), 1.78–1.70 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 3.7 Hz, 3H), 0.83 (d, J = 3.7 Hz, 6H) ppm. 

**13** C (¼ H) NMR (100 MHz, CDCl₃): δ 170.7, 154.9, 151.6, 116.2, 114.9, 80.6, 55.7, 46.4, 31.0, 28.5, 19.94, 19.90, 19.3, 18.7 ppm. IR (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₃₁H₄₂N₂O₅S: 510.5; Found, 510.18.

![Diagram](https://https://doi.org/10.1021/acs.joc.4c01057)

### (2R,3R)-1-(N-Isobutyl-P-nitrophenylsulfonamido)-2-(p-methoxyphenoxo)-p-methyl-p-nitrobenzensulfonate (32)

To a vigorously stirring solution of 31 (1.92 g, 6.50 mmol) in dichloromethane (23 mL) in a round-bottom flask was added p-nitrobenzenesulfonyl chloride (3.60 g, 16.2 mmol), followed by DMAP (0.874 g, 7.15 mmol). Triethylamine (3.60 mL, 25.8 mmol) was then added dropwise to the reaction mixture via an addition funnel. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with dichloromethane (50 mL) and washed with an aqueous solution of 1 M HCl (25 mL) and brine (25 mL). The organic layer was then isolated and dried over MgSO₄ and concentrated under reduced pressure to afford a crude yellow viscous oil that was crystallized from diethyl ether and hexanes to afford 32 (2.45 g, 57% yield) as yellow crystals. Mp: 132.6–133.9 °C. 

**1** H NMR (500 MHz, CDCl₃): δ 8.19 (dd, J = 14.1, 8.9 Hz, 4H), 7.98 (d, J = 8.9 Hz, 2H), 7.87 (d, J = 8.9 Hz, 2H), 6.62 (d, J = 9.1 Hz, 2H), 6.51 (d, J = 9.1 Hz, 2H), 4.66–4.63 (m, 1H), 4.55 (t, J = 5.9 Hz, 1H), 3.73 (s, 3H), 3.67 (dd, J = 15.3, 1.8 Hz, 1H), 3.4 (dd, J = 15.3, 9.3 Hz, 1H), 3.11 (dd, J = 13.8, 8.9 Hz, 1H), 2.99 (dd, J = 13.8, 6.9 Hz, 1H), 2.06–1.93 (m, 2H), 1.02 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H) ppm. 

**13** C (¼ H) NMR (100 MHz, CDCl₃): δ 154.7, 150.6, 150.5, 149.8, 145.6, 142.0, 129.0, 128.1, 124.3, 121.4, 116.2, 114.5, 86.8, 57.0, 55.6, 48.5, 29.0, 26.5, 19.8, 19.7, 18.2 ppm. IR (CDCl₃): 3108, 1607, 1350, 855 cm⁻¹. HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₃₀H₂₃N₂O₅S: 688.1605; Found, 688.1605.
A round-bottom flask containing compound 34 (0.100 g, 0.250 mmol), 5% palladium on carbon (0.001 g), 2,5-dioxopyrrolidin-1-yl-(3R,3aS,6aR)-hexahydropyran-3-ylcarbonate (0.0611 g), and THF (8.30 mL) was flushed with N₂ gas for 10 min. A balloon filled with H₂ gas was then connected to the reaction flask, and the mixture was allowed to stir overnight at room temperature. After completion, the reaction mixture was diluted with chloroform, filtered through a 1:1 mixture of Celite and MgSO₄, and concentrated under reduced pressure to afford a dark-red viscous oil. The residue was purified by flash column chromatography (2:8, diethyl ether-hexane) to afford β-azido alcohol 34 (0.399 g, 0.99 mmol, 45% yield) as a dark-red viscous oil. ¹H NMR (500 MHz, CDCl₃): δ 8.39 (d, J = 8.9 Hz, 2H), 8.02 (d, J = 8.9 Hz, 2H), 3.88 (broad triplet, J = 8.9 Hz, 1H), 3.31 (dd, J = 15.2, 9.6 Hz, 1H), 3.19 (t, J = 6.2, Hz, 1H), 3.15 (dd, J = 15.2, 2.2 Hz, 1H), 3.09 (dd, J = 13.6, 8.2 Hz, 1H), 2.98 (dd, J = 13.6, 7.1 Hz, 2H), 2.0–1.87 (m, 2H), 1.04 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H). IR (CDCl₃, ν): 3519, 3107, 2104, 1607, 1531, 1350, 856 cm⁻¹. HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for C₁₇H₂₆N₄O₃NaS 424.1469; Found, 424.1469.

(3R,3aS,6aR)-Hexahydropyran-3-yl(2R,3S)-(4-amino-N-isobutylphenyl sulfonamido)-2-hydroxy-4-methylpentan-3-yl(carbamat) (35). A round-bottom flask containing compound 34 (0.100 g, 0.250 mmol), 5% palladium on carbon (0.001 g), 2,5-dioxopyrrolidin-1-yl-(3R,3aS,6aR)-hexahydropyran-3-ylcarbonate (0.0611 g), and THF (8.30 mL) was flushed with N₂ gas for 10 min. A balloon filled with H₂ gas was then connected to the reaction flask, and the mixture was allowed to stir overnight at room temperature. After completion, the reaction mixture was diluted with chloroform, filtered through a 1:1 mixture of Celite and MgSO₄, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (18:85, diethyl ether-hexane) to afford aldol adduct 39 (10.62 g, 25.0 mmol, 82% yield) as a pale-yellow viscous oil. [α]D = +70.4 (c = 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.34–7.29 (m, 3H), 7.23–7.21 (m, 2H), 6.67 (d, J = 2.0 Hz, 1H), 6.66–6.61 (m, 4H), 5.68 (dd, J = 8.3, 2.5 Hz, 1H), 4.84 (t, J = 8.7 Hz, 1H), 4.53–4.47 (m, 2H), 3.70 (s, 3H), 1.71 (dd, J = 14.7, 9.5 Hz, 1H), 1.61 (dd, J = 14.6, 2.0 Hz, 1H), 1.02 (s, 9H), ppm. ¹C¹H (¹H) NMR (100 MHz, CDCl₃): 158.4, 169.6, 154.5, 151.3, 138.3, 139.2, 128.9, 125.8, 116.2, 114.6, 80.2, 74.7, 70.2, 62.8, 55.7, 47.8, 30.5, 30.2 ppm. IR (CDCl₃): 3422, 1716, 1507, 1228, 1196, 824 cm⁻¹. HRMS (ESI-TOF) m/z: [M + H⁺]+ Calcd for C₂₃H₃₉N₄O₅S 444.1839; Found, 444.1838.

(3R,3aS,6aR)-Hexahydropyran-3-yl(2R,3S)-1-(4-amino-N-isobutylphenyl sulfonamido)-2-hydroxy-4-methylpentan-3-yl(carbamat) (35). A round-bottom flask containing compound 34 (0.100 g, 0.250 mmol), 5% palladium on carbon (0.001 g), 2,5-dioxopyrrolidin-1-yl-(3R,3aS,6aR)-hexahydropyran-3-ylcarbonate (0.0611 g), and THF (8.30 mL) was flushed with N₂ gas for 10 min. A balloon filled with H₂ gas was then connected to the reaction flask, and the mixture was allowed to stir overnight at room temperature. After completion, the reaction mixture was diluted with chloroform, filtered through a 1:1 mixture of Celite and MgSO₄, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (18:85, diethyl ether-hexane) to afford aldol adduct 39 (10.62 g, 25.0 mmol, 82% yield) as a pale-yellow viscous oil. [α]D = +70.4 (c = 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.34–7.29 (m, 3H), 7.23–7.21 (m, 2H), 6.67 (d, J = 2.0 Hz, 1H), 6.66–6.61 (m, 4H), 5.68 (dd, J = 8.3, 2.5 Hz, 1H), 4.84 (t, J = 8.7 Hz, 1H), 4.53–4.47 (m, 2H), 3.70 (s, 3H), 1.71 (dd, J = 14.7, 9.5 Hz, 1H), 1.61 (dd, J = 14.6, 2.0 Hz, 1H), 1.02 (s, 9H), ppm. ¹C¹H (¹H) NMR (100 MHz, CDCl₃): 158.4, 169.6, 154.5, 151.3, 138.3, 139.2, 128.9, 125.8, 116.2, 114.6, 80.2, 74.7, 70.2, 62.8, 55.7, 47.8, 30.5, 30.2 ppm. IR (CDCl₃): 3422, 1716, 1507, 1228, 1196, 824 cm⁻¹. HRMS (ESI-TOF) m/z: [M + H⁺]+ Calcd for C₂₃H₃₉N₄O₅S 444.1839; Found, 444.1838.
(2R,3R)-1-(Isobutylamino)-2-(p-methoxyphenoxy)-5,5-dimethyl-3-hexanol (42).\textsuperscript{29} To a flame-dried, nitrogen-purged 2 L round-bottom flask equipped with a magnetic stir bar were added amide 41 (6.64 g, 19.7 mmol) and THF (493 mL). A borane dimethylsulfide complex (5.60 mL) was added to the reaction mixture, and the reaction was then heated to reflux overnight using a heating mantle controlled by a variable transformer. The reaction was then cooled using an ice bath and quenched by the dropwise addition of methanol (30 mL). The reaction mixture was stirred for an additional 30 min, and the reaction solvent was removed via rotary evaporation. The concentrated reaction mixture was then diluted with diethyl ether (150 mL) and treated with an aqueous solution of 1 M NaOH (2 × 50 mL). The organic layer was washed one more time with brine (50 mL), dried over MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (7:3, diethyl ether:hexanes) to afford 42 (5.95 g, 18.3 mmol, 93% yield) as a colorless viscous oil. \textsuperscript{1}H NMR (500 MHz, CDCl\(_3\)): \(\delta 6.91 (d, J = 9.2 \text{ Hz}, 2H), 6.82 (d, J = 9.2 \text{ Hz}, 2H), 4.11 - 4.06 (m, 2H), 3.76 (s, 3H), 3.19 (dd, \(J = 12.5, 5.2 \text{ Hz}, 1H), 2.85 (dd, \(J = 12.5, 3.2 \text{ Hz}, 1H), 2.43 - 2.36 (m, 2H), 1.75 - 1.64 (m, 1H), 1.59 (dd, \(J = 14.4, 8.5 \text{ Hz}, 1H), 1.45 (dd, \(J = 14.5, 2.2 \text{ Hz}, 1H), 0.97 (s, 9H), 0.89 (d, \(J = 2.8 \text{ Hz}, 1H) \text{ ppm.} \textsuperscript{13}C\text{[H]}\text{NMR (100 MHz, CDCl}_3\text{):} \delta 154.3, 152.1, 117.4, 114.7, 79.9, 71.8, 58.2, 55.7, 50.7, 47.0, 30.2, 30.1, 28.2, 20.5, 20.5 ppm. IR (CDCl\(_3\)): 3322, 1227, 1042, 827 cm\(^{-1}\). HRMS (ESI-TOF) m/z: [M + H]\textsuperscript{+} Calcd for C\(_{19}\)H\(_{34}\)NO\(_3\) 324.2533; Found, 324.2538.

\(\text{N-[(2R,3R)-3-Hydroxy-2-(p-methoxyphenoxy)-5,5-dimethylhex-yl]-N-isobutyl-4-nitrobenzene sulfonamide (43).}\textsuperscript{29} To a stirred solution of compound 42 (5.20 g, 16.1 mmol) and dichloromethane (54 mL) in a round-bottom flask was added p-nitrobenzenesulfonyl chloride (8.91 g, 40.2 mmol), followed by DMAP (2.16 g, 17.7 mmol). Once all the reaction components had dissolved, triethylamine (8.80 mL, 63.1 mmol) was then added dropwise via an addition funnel. The reaction mixture was then allowed to stir overnight at room temperature. After completion, the reaction mixture was diluted with dichloromethane and treated with an aqueous solution of 1 M HCl (2 × 30 mL). The organic layer was treated with brine (30 mL), dried over MgSO\(_4\) and concentrated under reduced pressure to afford a crude yellow viscous oil. The residue was purified by flash column chromatography on silica gel (7:3, diethyl ether:hexanes) to afford 43 (3.95 g, 5.70 mmol, 77% yield) as a yellow viscous oil. \textsuperscript{1}H NMR (500 MHz, CDCl\(_3\)): \(\delta 8.38 (d, J = 9.0 \text{ Hz}, 2H), 8.12 (dd, \(J = 9.0, 5.0 \text{ Hz}, 4H), 7.92 (d, \(J = 9.0 \text{ Hz}, 2H), 7.60 (d, J = 9.0 \text{ Hz}, 2H), 6.71 (d, J = 9.1 \text{ Hz}, 2H), 6.59 (d, J = 9.1 \text{ Hz}, 2H), 4.95 (dd, \(J = 9.0, 4.1, 1.1 \text{ Hz}, 1H), 4.77 (ddd, \(J = 9.7, 4.1, 1.5 \text{ Hz}, 2H), 3.73 (s, 3H), 3.72 (d, \(J = 15.1, 1.4 \text{ Hz}, 1H), 3.51 (dd, \(J = 15.5, 9.7 \text{ Hz}, 1H), 3.28 (dd, \(J = 13.7, 8.3 \text{ Hz}, 1H), 3.12 (dd, \(J = 13.7, 6.8 \text{ Hz}, 1H), 2.10 - 2.02 (m, 1H), 1.71 (dd, \(J = 15.3, 1.1 \text{ Hz}, 1H), 1.43 (dd, \(J = 15.3, 9.2 \text{ Hz}, 1H), 0.93 (dd, \(J = 6.7, 1.8 \text{ Hz}, 1H), 0.74 (s, 9H) \text{ ppm.} \textsuperscript{13}C\text{[H]}\text{NMR (100 MHz, CDCl}_3\text{):} \delta 154.8, 150.9, 149.6, 149.5, 146.3, 142.0, 129.3, 128.0, 124.5, 124.1, 116.2, 114.7, 77.7, 75.4, 56.2, 55.6, 46.2, 40.6, 29.9, 29.3, 26.4, 19.8, 19.7 ppm. IR (CDCl\(_3\)): 3108, 1607, 1532, 1350, 829 cm\(^{-1}\). HRMS (ESI-TOF) m/z: [M + H]\textsuperscript{+} Calcd for C\(_{33}\)H\(_{40}\)N\(_2\)S\(_2\)O\(_4\) 694.2099; Found, 694.2090.

\(\text{N-[(2R,3S)-3-Azido-2-(p-methoxyphenoxy)-5,5-dimethylhex-y1]-N-isobutyl-4-nitrobenzene sulfonamide (45).}\textsuperscript{29} To a stirring solution of compound 44 (3.73 g, 5.37 mmol) in DMSO (36 mL) was added sodium azide (1.40 g). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was diluted with diethyl ether (100 mL) and washed with an aqueous solution of 1 M HCl (2 × 30 mL). The organic layer was washed one more time with brine, dried over MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with dichloromethane to afford azide 45 (2.615 g, 91% yield) as a yellow viscous oil. \textsuperscript{1}H NMR (500 MHz, CDCl\(_3\)): \(\delta 8.24 (d, J = 8.9 \text{ Hz}, 2H), 7.95 (d, J = 8.9 \text{ Hz}, 6.77 (d, J = 9.2 \text{ Hz}, 2H), 6.69 (d, J = 9.2 \text{ Hz}, 2H), 4.41 (dt, \(J = 9.3, 2.4 \text{ Hz}, 2H), 3.76 (s, 3H), 3.71 (dt, \(J = 8.1, 2.6 \text{ Hz}, 1H), 3.56 (dd, \(J = 15.6, 2.0 \text{ Hz}, 1H), 3.41 (dd, \(J = 15.6, 9.1 \text{ Hz}, 1H), 3.25 (dd, \(J = 13.5, 8.6 \text{ Hz}, 1H), 2.97 (dd, \(J = 13.5, 6.5 \text{ Hz}, 1H), 2.09 - 2.01 (m, 1H), 1.33 (dd, \(J = 14.5, 2.7 \text{ Hz}, 1H), 1.29 (dd, \(J = 14.5, 8.1 \text{ Hz}, 1H), 0.93 (s, 9H), 0.89 (d, \(J = 6.6 \text{ Hz}, 3H) \text{ ppm.} \textsuperscript{13}C\text{[H]}\text{NMR (100 MHz, CDCl}_3\text{):} \delta 154.8, 149.9, 149.8, 145.7, 128.2, 124.2, 116.9, 114.9, 81.7, 59.4, 57.5, 55.6, 48.1, 43.8, 30.4, 29.4, 26.6, 20.0, 19.9 ppm. IR (CDCl\(_3\)): 3106, 2115, 1606, 1531, 1350, 827 cm\(^{-1}\). HRMS
To a stirred solution of 45 (2.12 g, 3.96 mmol) in CH₂CN (46.5 mL) was added cerium (IV) ammonium nitrate (4.35 g, 7.93 mmol), followed by deionized water (15.5 mL). The reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was then diluted with diethyl ether (100 mL), washed with brine (2 × 30 mL), dried over MgSO₄ and concentrated under reduced pressure to afford a dark-red viscous oil. The residue was purified by flash column chromatography on silica gel (2:8, diethyl ether:hexane) to afford azide 46 (0.6406 g, 38% yield) as a dark-red viscous oil. ¹H NMR (500 MHz, CDCl₃): δ 8.39 (d, J = 8.9 Hz, 2H), 8.02 (d, J = 8.9 Hz, 2H), 3.81 (broad singlet, 1H), 3.39 (dd, J = 9.1, 4.8, 2.0 Hz, 1H), 3.33 (t, J = 15.3, 9.5 Hz, 1H), 3.13−3.04 (m, 3H), 2.97 (dd, J = 13.6, 7.0 Hz, 1H), 1.95−1.86 (m, 1H), 1.44 (dd, J = 14.6, 2.0 Hz, 1H), 1.31 (dd, J = 14.6, 9.2 Hz, 1H), 0.98 (s, 9H), 0.95 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H) ppm. ¹³C (¹H) NMR (100 MHz, CDCl₃): δ 150.2, 144.6, 128.6, 124.5, 73.7, 62.7, 58.2, 51.7, 43.3, 30.1, 29.6, 27.1, 20.1, 19.8 ppm. IR (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₂₃H₂₃N₅NaO₈S 556.2200; Found, 556.2205.

N-((2R,3S)-3-Azido-2-hydroxy-5,5-dimethylhexyl)-N-isobutyl-p-nitrobenzenesulfonylamide (46).²⁹ A flame-dried 250 mL round-bottom flask containing compound 46 (0.424 g, 0.992 mmol), 5% palladium on carbon (0.005 g), 2,5-dioxopyrrolidin-1-yl((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)carbonate (0.242 g, 0.890 mmol), and THF (33 mL) was flushed with nitrogen gas for 10 min. A balloon filled with hydrogen gas was then connected to the reaction flask, and the mixture was allowed to stir overnight at room temperature. The reaction mixture was diluted with chloroform, filtered through a 1:1 mixture of Celite and MgSO₄, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with diethyl ether as the mobile phase to afford the desired 38 (0.4139 g, 0.784 mmol, 78% yield) as a pale-yellow viscous oil. [α]D = −193 (c = 1.00, CDCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.56 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 5.71 (d, J = 5.2 Hz, 1H), 5.12−5.16 (m, 1H), 5.01 (d, J = 9.3 Hz, 1H), 4.20 (brs, 2H), 4.28 (dd, J = 9.5, 6.4 Hz, 1H), 3.94 (d, J = 8.3, 2.75 Hz, 1H), 3.85−3.90 (m, 1H), 3.74 (d, J = 9.5, 6.7 Hz, 2H), 3.59−3.65 (m, 1H), 3.37 (d, J = 3.0 Hz, 1H), 3.13−3.02 (m, 2H), 2.96−2.90 (m, 2H), 2.81 (d, J = 13.4, 6.9 Hz, 1H), 2.02−1.97 (m, 1H), 1.89−1.80 (m, 2H), 1.57 (d, J = 14.6 Hz, 1H), 1.32−1.25 (m, 1H), 9.33 (s, 9H), 0.92 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H) ppm. ¹³C (¹H) NMR (125 MHz, CDCl₃): δ 155.3, 151.5, 129.3, 125.3, 113.9, 109.2, 74.0, 73.2, 70.7, 69.4, 58.2, 52.9, 51.8, 45.2, 43.2, 30.1, 29.7, 27.0, 25.8, 20.1, 20.0 ppm. IR (CDCl₃): 3459, 3364, 3254, 1706, 1147, 1090, 831 cm⁻¹. HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₃₆H₅₄N₅O₂S 528.2738; Found, 528.2743.

### ASSOCIATED CONTENT

**Data Availability Statement**

The data underlying this study are available in the published article and its Supporting Information.

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01057.

¹H and ¹³C NMR spectroscopic data for all reported compounds. X-ray crystallographic data for (R,S,R)-10 are provided (PDF)

### Accession Codes

CCDC 2285488 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033.

### AUTHOR INFORMATION

**Corresponding Author**

Shawn R. Hitchcock — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States; orcid.org/0000-0001-8514-7316; Email: hitchcock@ilstu.edu

**Authors**

Jordan M. Witte — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Emmanuel Ayim — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Christopher J. Sams — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Jasmine B. Service — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Caitlyn C. Kant — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Lillian Bambalas — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Daniel Wright — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Austin Carter — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Kelly Moran — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Isabella G. Rohrig — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Gregory M. Ferrence — Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acs.joc.4c01057

**Author Contributions**

*J.M.W. and E.A. contributed equally to the work. C.J.S. and J.B.S. made important contributions to original project development. All authors contributed to the development of this work. G.M.F. and I.G.R. contributed to the SCXRD analyses for structure (R,S,R)-10.*
The authors thank the NSF for funding the X-ray diffractometer.
