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TETRAHEDRON: *ASYMMETRY*

Total synthesis of a second generation HIV protease inhibitor

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Abstract—An efficient stereoselective preparation of HIV protease inhibitor (+)-**1** was synthesized on multi-kilogram scale in 16 steps without the use of chromatography. The key steps include the diastereoselective alkylation of acetal **3**, a diastereoselective iodo-hydroxylation to generate epoxide **6**, and a reductive amination in the final coupling step that averts a non-productive cyclic aminal intermediate.

1. Introduction

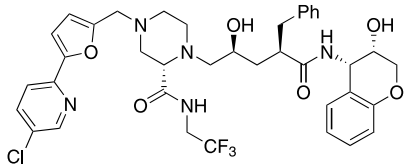
Intense research into the therapeutic intervention of AIDS has brought to market several orally active HIV protease inhibitors.[1,2] In combination with reverse transcriptase inhibitors, HIV aspartic protease inhibition has slowed the progression of HIV infection in AIDS patients.[3] However, current therapy may be in jeopardy due to fast emerging mutation and the accumulation of resistant strains.[4,5] As part of our program to develop practical syntheses of potentially new therapeutics for the treatment of HIV, we report here a process scale synthesis of a second generation orally active protease inhibitor **1**, which has shown to be sensitive to resistant strains.[6–8] Similar to existing protease inhibitors, high therapeutic doses of drug are anticipated, thus emphasis has been placed upon supply and cost effectiveness of the synthesis.

2. Results and discussion

Compound **1** is structurally similar to indinavir[9,10] with regard to the hydroxyaminobenzylpentane amide backbone and the piperazine amide core (Fig. 1). However, major differences are noted with the replacement of aminoindanol with aminochromanol and the 3-picolyl segment with a biaryl 2′-pyridine-furanyl substituent. Retrosynthetically, the structure is disconnected into biaryl aldehyde **16**, piperazine **12**, and epoxide **6**. Epoxide **6** is further disconnected to *cis*-aminochromanol (Scheme 1).

2.1. Synthesis of epoxide 6

The synthesis begins with the resolution of *cis*-aminochromanol **2**,[11] which was successfully achieved via classical resolution using (*S*)-mandelic acid (Scheme 2). A method similar to that developed by Maligres et al.[12] was used to relay the stereochemical information of *cis*-aminochromanol into the hydroxyaminobenzylpentane amide side chain.



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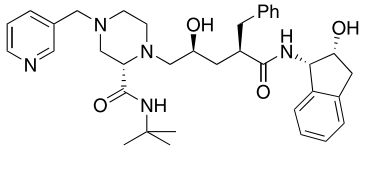

Indinavir

Figure 1.

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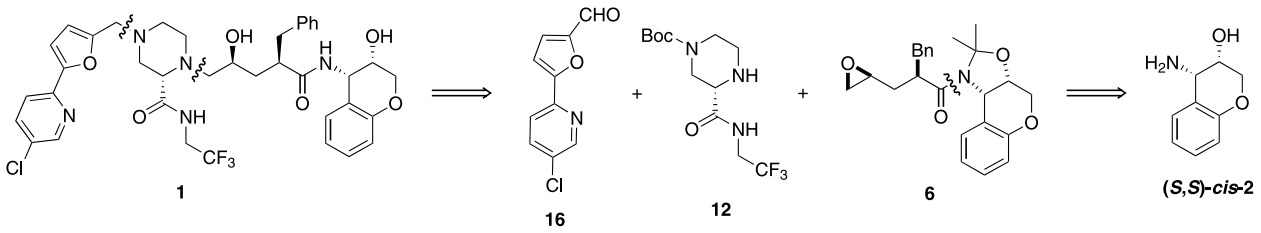
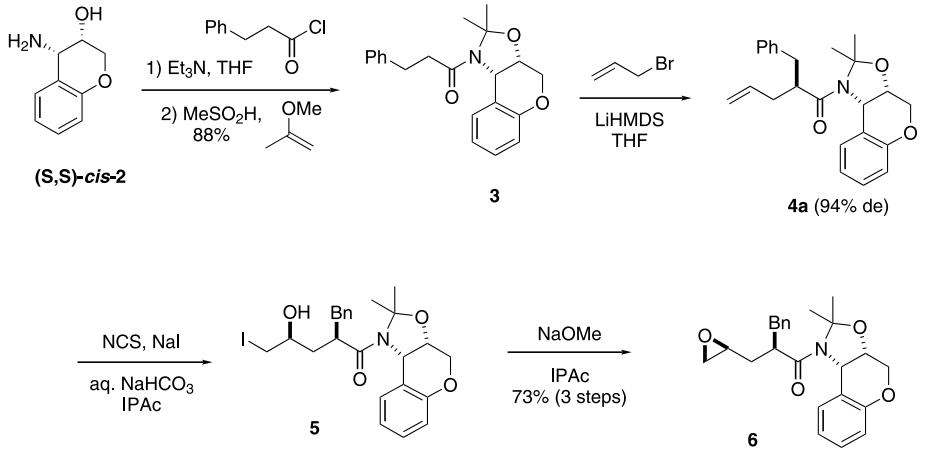


Scheme 1. Retrosynthesis of HIV protease inhibitor **1**.



Scheme 2. Synthesis of epoxide **6**.

(*S*,*S*)-*cis*-Aminochromanol **2** was acylated with hydrocinnamoyl chloride to give a hydroxyamide intermediate, which was ketalized in a one-pot process to provide acetonide **3**. Using a slight excess of hydrocinnamoyl chloride (1.05 equiv.) and triethylamine as base provided the hydroxyamide in nearly quantitative yield at 23°C. Acetonide **3** was generated using 2-methoxypropene and methanesulfonic acid (MSA). Other acid catalysts such as pyridinium *p*-toluenesulfonate and *p*-toluenesulfonic acid and 2,2-dimethoxypropane reagent were less effective. The reaction was complete in 5 h at 60°C using 4 equiv. 2-methoxypropene and 0.1 equiv. MSA. Acylation was performed at 40–45°C to maintain a thin slurry of hydroxyamide. Before adding the low boiling 2-methoxypropene (34–36°C), the temperature was lowered to 30°C where the slurry was thicker but manageable, then the temperature was increased gradually to 60°C and aged until the reaction was complete. Acetonide **3** was isolated as a white crystalline solid with >99% purity by HPLC in 88% yield. Using aminochromanol of lesser enantiomeric excess (e.g. 95% ee) still afforded acetonide **3** with >99% ee after crystallization.

The acetonide **3** was deprotonated with LHMDS and alkylated with allyl bromide to afford olefin **4a** and its diastereomer **4b** in 97:3 ratio. The reaction was quenched with citric acid, solvent switched from THF to isopropyl acetate (IPAc), and washed with dilute sulfuric acid followed by aqueous sodium bicarbonate to afford a solution of olefin in IPAc which was used in the subsequent iodination step. The reaction was conducted at −25°C to maximize yield and minimize the formation of the acetone elimination impurity **7** as well as the acetone adduct **8** (Fig. 2).

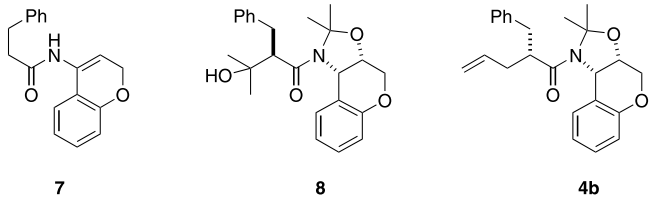


Figure 2. Alkylation impurities.

The solution of olefin **4** in IPAc was treated with *N*-iodosuccinimide (NIS) and aqueous $NaHCO_3$ to afford the iodohydrin **5** after 18 h at 23°C. Due to the prohibitive cost of NIS, on scale NIS was prepared in situ from *N*-chlorosuccinimide (NCS) and NaI.[13,14] Comparable results were obtained as with NIS. The reaction was performed successfully on kilogram scale with >99.9% conversion to product and 84% assay yield.

Epoxide **6** was generated by treating the solution of iodohydrin in IPAc with NaOMe in methanol. Using 1.4 equiv. NaOMe, the reaction was rapid and gave >99.5% conversion within 0.5 h. After quenching with water, the aqueous layer was cut and the organic layer was washed with 10% aqueous Na_2SO_4 to lower the pH to 5–6. If the water quench was performed at 23°C, the reaction slowly reverted back to iodohydrin **5**. This

back reaction was minimized by maintaining the reaction at 10–15°C during the quench, and >98% conversion was consistently achieved after the workup. The crude solution of epoxide in IPAc was solvent switched to IPA, and then warmed to 70°C to dissolve all the solids. The solution was then cooled slowly to crystallize the epoxide **6**. This crystallization rejected the impurities that had accumulated over the three steps from the acetonide **3**, and the epoxide **6** was isolated with >98% purity by HPLC and in 78% overall yield from the acetonide **3**.

2.2. Synthesis of BOC-piperazine amide 12

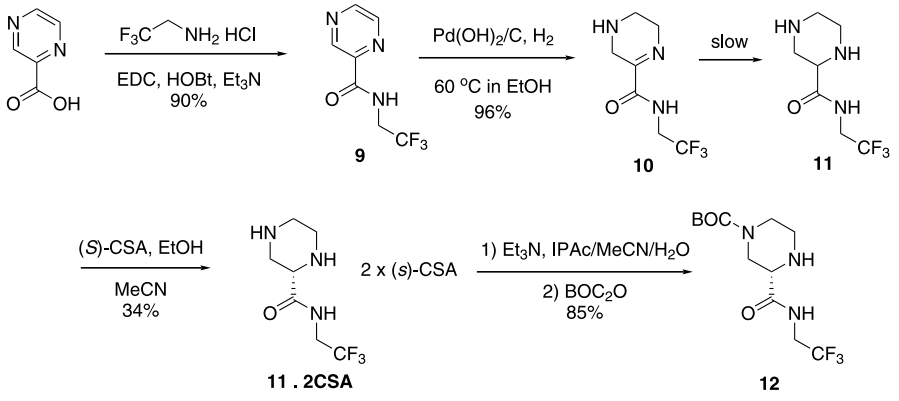
Standard peptide coupling of pyrazine-2-carboxylic acid with trifluoroethylamine HCl gave the pyrazine amide **9**, which was then exhaustively reduced to the piperazine amide **11** using Pearlman's catalyst [$Pd(OH)_2$] (Scheme 3). Interestingly, reaction calorimetry data showed two distinct kinetic regimes: an initial very fast regime corresponding to formation of the tetrahydropyrazine **10** followed by a slow regime corresponding to conversion of **10** to the desired piperazine amide. The initial regime gives a fast heat release with an adiabatic temperature rise of ≥ 35. This initial, fast heat released is managed at large scale by starting the hydrogenation at reduced temperature with low hydrogen pressure. The stepwise nature of the reduction may allow for asymmetric induction since reductions of tetrahydropyrazines have been shown to proceed with good enantioselectivity.[15] Unfortunately, the chemical instability of tetrahydropyrazine **10** precluded exploration into reduction by asymmetric catalysts. On scale, the racemic piperazine amide **11** was successfully resolved via a classical resolution with (1*S*)-(+)-10-camphorsulfonic acid (CSA). The desired **11** bis (*S*)-CSA salt was isolated in 34% yield and >98%ee.

The bis (*S*)-CSA salt of **11** was free based with triethylamine in IPAc/MeCN in the presence of a small amount of water (1.25%) and then treated with di-*tert*-butyl dicarbonate (1.0 equiv.). The water was necessary to prevent bis BOC formation (typically <3%) due to the precipitation of the mono CSA salt of **11**. After aqueous workup and solvent switching to IPA, the crude solution of mono BOC-piperazine amide **12** assayed at 85% yield and was used directly in the subsequent epoxide opening step.

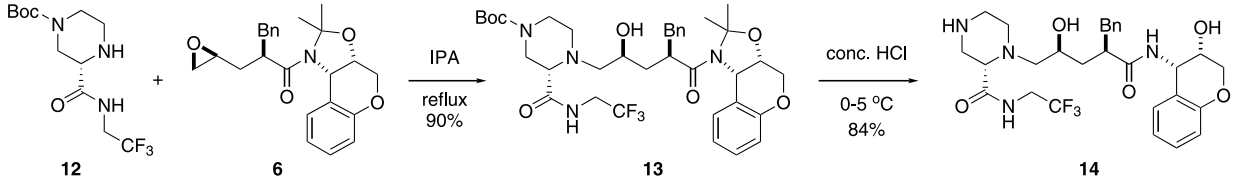
2.3. Epoxide opening and formation of penultimate 14

The coupling of epoxide **6** with BOC-piperazine amide **12** in refluxing IPA afforded the adduct **13** (Scheme 4). A variety of solvents and Lewis acid catalysts were investigated. The alcohol solvents (MeOH, EtOH, IPA, *n*-PrOH) showed the best reaction profile, although the reaction was slow. IPA was chosen for this reaction since it allowed for heating at higher temperatures and because less solvolysis of the epoxide was observed with this secondary alcohol. Using a slight excess of **12** (1.05 equiv.) and running the reaction more concentrated increase the reaction rate, and 98% conversion and 90% assay yield by HPLC was achieved after 30–48 h at reflux.

The acetonide and BOC protecting groups were removed by adding conc. HCl at 0–5°C. The BOC group decomposed rapidly liberating CO_2 and isobutylene, followed by slower deketalization. Some decomposition of **14** was detected by the presence of amide hydrolysis and cyclization byproducts (Fig. 3).



Scheme 3. Synthesis of BOC-piperazine amide **12**.



Scheme 4. Synthesis of penultimate **14**.

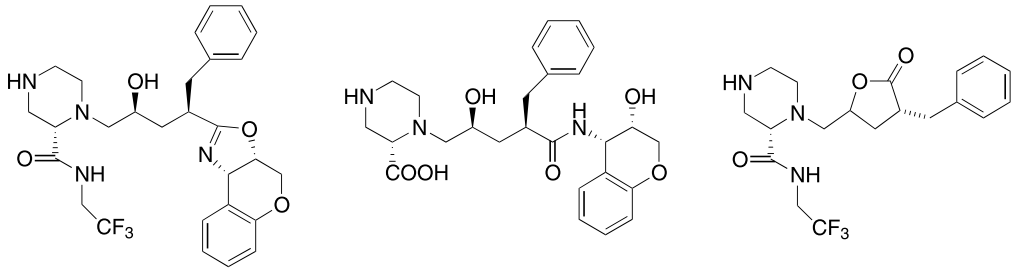


Figure 3. Impurities formed during deprotection of **13**.

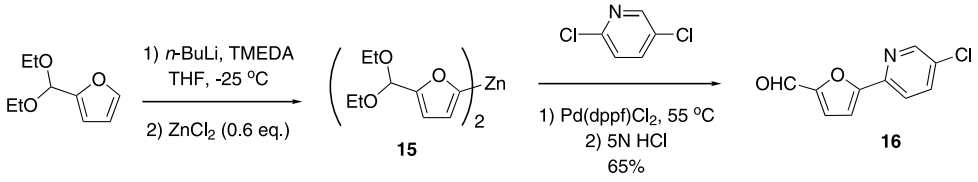
2.4. Synthesis of biaryl aldehyde 16

Biaryl aldehyde **16** was prepared by a four step, two pot process (Scheme 5): deprotonation, transmetallation, Pd-catalyzed cross-coupling, and deprotection/crystallization).[16] Several issues needed to be addressed before this chemistry could be executed on scale: attenuation of the extreme cryogenics (−78°C), reduction of water in commercial $ZnCl_2$, and product isolation without chromatography. Introduction of TMEDA in the deprotonation of furaldehyde diethyl acetal imparted stability up to −15°C.

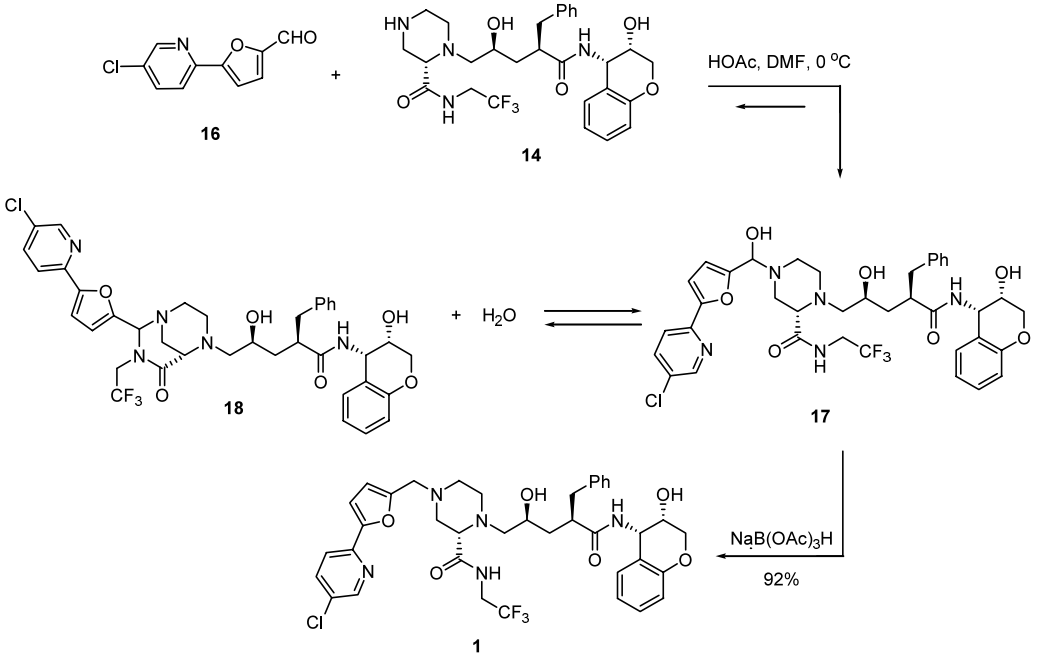
Commercial anhydrous $ZnCl_2$ contains 1–2% water, thus drying was necessary before use. Dissolution in THF followed by molecular sieve drying was impractical due to the excessive volume of THF necessary to dissolve $ZnCl_2$. Thus, a slurry of 1.5–2 M $ZnCl_2$ in THF was dried via azeotropic distillation. The $ZnCl_2$ drying requirements were significantly reduced by lowering the $ZnCl_2$ charge (0.6 equiv. versus 1.2 equiv.), which generated diorganozinc **15**.[17] After cross-coupling with 2-chloropyridine the resulting biaryl acetal was deprotected. Attempts to directly crystallize crude aldehyde **16** failed due to the precipitation of a black tarry oil rich in Zn, Pd, and product. Thus, the crude acetal solution was treated with activated carbon which removed highly colored impurities and residual metals. After filtration, the solution of acetal was treated with 5N HCl to impart concomitant deprotection and crystallization. Biarylaldehyde **16** was isolated in 65% yield from furfuraldehyde diethyl acetal with >98% purity by HPLC.

2.5. Endgame coupling: reductive amination to form HIV protease inhibitor 1

The reductive-amination of penultimate **14** with biaryl aldehyde **16** provided a near quantitative assay yield of **1** using sodium triacetoxyborohydride (STAB) and acetic acid in DMF (Scheme 6). However, in preparation for kilo-scale, experiments involving extended aging at various temperatures delineated a non-productive pathway that ultimately provide starting materials **14** and **16** after aqueous work up. The initial combination of **14** and **16** in DMF at 23°C provided a mixture of starting materials plus N,O-acetal **17**. Upon addition of acetic acid at 23°C bicyclic aminal amide **18** was formed, which was unreactive to STAB. The identity of **18** is based upon detailed NMR analysis of a mixture **14**, **16** and HOAc in DMF-d_7 which after aging at 23°C gave ~60% conversion to **18** as a single diastereomer (see Section 4). Conclusive evidence for the structural assignment was generated using the 2-D HMBC (Heteronuclear Multiple Bond Correlation) experiment, which showed a three-bond correlation between the non-equivalent CF_3CH_2-methylene protons (4.95 and 3.57 ppm) and the aminal methine carbon at 75.1 ppm. Process parameters were developed to minimize aminal formation in a timeline amenable to kilo scale processing. The penultimate and aldehyde were dissolved in DMF at 23°C to pre-form the hemi-aminal **17**. The reaction was then cooled to 0°C and HOAc was added while maintaining the temperature below 5°C. Since HOAc slowly promotes aminal formation even at 0°C, HOAc was added as quickly as possible (<15 min) followed immediately by STAB. After STAB addition, the reaction was warmed to 23°C over 0.5 h. Aminal formation was typically less than 2% by HPLC using this procedure, and after crystallization via the addition of water, the free base was isolated in 92% yield. Further removal of processing impurities was necessary. Thus, the crude free base was dissolved in hot MeOH, treated with decolorizing charcoal and then recrystallized. Due to the insolubility of **1** in water (<0.1 mg/mL), the bis benzenesulfonic acid salt was generated to increase oral bioavailability.



Scheme 5. Synthesis of biarylaldehyde **16**.



Scheme 6. Endgame: Reductive amination to form compound **1**.

3. Conclusion

In summary, introduction of asymmetry into compound **1** relied on classical resolution to prepare *cis*-aminochomanol **2** and BOC-piperazine amide **12**, which ultimately comprised three of the five stereocenters in **1**. *Cis*-aminochromanol derived amide **3** affected two successive diastereoselective steps: allylation followed by iodolactonization, which introduced the remaining two stereocenters in the form of epoxide **6**. A four-step, two-pot procedure was developed to prepare biarylaldehyde **16**, which was then efficiently coupled with penultimate **14** via reductive amination. We have achieved a practical asymmetric synthesis of orally active protease inhibitor **1** in 16 chemical steps, all of which have been demonstrated on multi kilogram scale.

4. Experimental

4.1. General experimental

Melting points were determined using a Büchi B-545 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Magna-FT-IR 560 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer. HPLC analyses were performed on a Hewlett Packard Series 1100 chromatograph. GC-MS analyses were performed on a Hewlett Packard Series 6890 chromatograph equipped with a Hewlett Packard 5973 Mass Selective Detector. HRMS was performed on a Finnigan New-Star FT/ICR instrument via ESI. KF titrations were performed on a Brinkmann 737 KF Coulometer (anode solution: Hydranal-Coulomat AG; cathode solution: Aqua Star—Coulomat CK). All reagents and starting materials were obtained from commercial suppliers and used without further purification. If necessary, solvents were dried by recycling through a bed of 4 Å molecular sieves until KF value was <500 ug/mL.

HPLC conditions

Method A: Column: Waters Xterra RP8, 5 μm, 4.6 mm×250 mm (Waters Corporation, Milford, MA); detection wavelength (λ): 220 nm; The solvent system was a gradient of solvent A (aqueous 5 mM K_2HPO_4 pH adjusted to 8.0 with H_3PO_4) and solvent B (CH_3CN) applied as follows: isocratic, 5% B, 0–5 min; linear, 60% B, 5–20 min; linear, 70% B, 20–25 min; flow rate: 1.5 mL/min; temperature: 25°C.

Method B: Column: YMC Basic Column, 5 μm, 4.6 mm×250 mm (Waters Corporation, Milford, MA); detection wavelength (λ): 210 nm; The solvent system was a gradient of solvent A (0.1% H_3PO_4) and solvent B (CH_3CN) applied as follows: linear, 5% B to 60% B, 0–20 min; isocratic 60% B, 20–22 min; flow rate: 1.5 mL/min, temperature: 40°C.

Method C: Column: Chiral AGP, 4.0 mm×100 mm (Regis Technologies, Morton Grove, IL); detection wavelength (λ): 210 nm; The solvent system was a gradient of solvent A (aqueous 10 mM K_2HPO_4 pH adjusted to 6.5 with H_3PO_4) and solvent B (CH_3CN) applied as follows: isocratic, 3% B, 0–10 min; flow rate: 1.0 mL/min; temperature: 40°C.

Method D: Column: Zorbax RX-C8, 4.6 mm×250 mm (Agilent Technologies, Palo Alto, CA); detection wavelength (λ): 210 nm; The solvent system was composed of solvent A (aqueous 0.1% H_3PO_4) and solvent B (CH_3CN) applied as follows: isocratic, 60% B, 0–15 min; flow rate: 1.0 mL/min; temperature: 25°C.

Method E: Column: Zorbax RX-C8, 4.6 mm×150 mm (Agilent Technologies, Palo Alto, CA); detection wavelength (λ): 210 nm; The solvent system was a gradient of solvent A (aqueous 0.1% H_3PO_4) and solvent B (CH_3CN) applied as follows: linear, 5% B to 90% B, 0–12 min; flow rate: 1.0 mL/min; temperature: 25°C.

Method F: Column: Luna Phenyl-Hexyl, 3 μm, 4.6 mm×100 mm (Phenomenex, Torrance, CA); detection wavelength (λ): 280 nm; The solvent system was a gradient of solvent A (aqueous 1 mM K_2HPO_4 pH adjusted to 8.0 with H_3PO_4) and solvent B (CH_3CN) applied as follows: isocratic, 25% B, 0–8 min; linear, 80% B, 8–12 min; flow rate: 1.5 mL/min; temperature: 50°C.

Method G: Column: YMC Pro C-18, 5 μm, 120 Å pore, 4.6 mm×250 mm (Waters Corporation, Milford, MA); detection wavelength (λ): 210 nm; The solvent system was a gradient of solvent A (aqueous 2 mM K_2HPO_4 pH adjusted to 6.4 with H_3PO_4), solvent B (CH_3CN) and solvent C (MeOH) applied as follows: linear, 65:20:15 to 45:40:15, 0–5 min; linear, 35:50:15, 5–30 min; linear, 20:65:15, 30–40 min; flow rate: 1.5 mL/min; temperature: 25°C.

4.2. (3a*S*,9b*S*)-2,2-Dimethyl-1-(3-phenylpropanoyl)-1,3a,4,9b-tetrahydro-2*H*-chromeno-[4,3-*d*][1,3]oxazole 3

To a solution of (*S*,*S*)-aminochromanol (100 g, 605 mmol) and triethylamine (89 mL, 635 mmol) in dry THF (1.8 L) at rt was added a solution of hydrocinnamoyl chloride (93 mL, 622 mmol) in THF (200 mL) over 40 min and the temperature was allowed to drift up to 45°C. At the end of addition, a slurry was generated which was stirred at 45°C for 30 min then cooled to 30°C. 2-Methoxypropene (232 mL, 2.42 mol) was added, followed by methanesulfonic acid (4.0 mL, 62 mmol). The mixture was warmed gradually from 35 to 60°C and stirred 4 h at 60°C until the reaction was complete (<0.1 A% hydroxyamide remaining) as determined by HPLC (Method D). [Compound retention times: aminochromanol (2.1 min), hydroxyamide (3.9 min), acetonide (7.7 min)]. Then triethylamine (9 mL) was added. The mixture was concentrated and solvent switched to IPAC at 2.4 L volume. The mixture was cooled to rt and 5% $NaHCO_3$ (900 mL) was added. The aqueous layer was cut and the organic layer was washed with 5% $NaHCO_3$ (900 mL) and water (900 mL). The organic layer was concentrated to 2.5 L and solvent switched to cyclohexane. The slurry was heated to 80°C to form a clear solution, which was cooled over 3 h to 3°C. The resulting slurry was filtered and the solids were washed with cyclohexane (250 mL). After drying in a 50°C vacuum oven, 180 g (88% yield) of acetonide **3** was obtained. The ML loss was 6%. Mp = 122°C. $[\alpha]_D^{25} = +62$ (*c* 0.24, DCM). ^{1}H NMR (d_6 DMSO, 400 MHz) indicated a 3.8:1 mixture of rotamers: δ 7.31 (m, 5H), 7.13 (t, $J = 8$ Hz, 1H), 7.06 (d, $J = 8$ Hz, 1H), 6.82 (t, $J = 8$ Hz, 1H), 6.75 (d, $J = 8$ Hz, 1H), 5.24 (d, $J = 4$ Hz, 1H), 4.32 (d, $J = 13$ Hz, 1H), 4.18 (t, $J = 13$ Hz, 2H), 3.03 (m, 4H), 1.49 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (d_6 DMSO, 100 MHz): δ 24.5, 26.9, 31.7, 37.5, 52.8, 63.7, 70.5, 95.1, 116.8, 121.4, 121.8, 126.4, 128.4, 128.6, 129.0, 129.0, 141.3, 153.2, 169.0. Anal. calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.63; H, 6.84; N, 4.13.

4.3. (3a*S*,9b*S*)-1-[(2*S*)-2-Benzylpent-4-enoyl]-2,2-dimethyl-1,3a,4,9b-tetrahydro-2*H*-chromeno[4,3-*d*][1,3]-oxazole 4a

Acetonide **3** (50.0 g, 148 mol) was dissolved in dry THF (283 mL) and the solution was degassed and inerted under N_2. The solution was cooled to −45°C and allyl bromide (18.6 g, 154 mmol) was added. Lithium bis(trimethylsilyl)amide (1.38 M, 109 g, 169 mmol) was added and the mixture was stirred 2 h. HPLC assay (Method D) showed <0.2A% starting material remaining. (Compound retention times: allylbromide (5.2 min), acetone eliminated impurity (6.0 min), acetone adduct (7.2 min), acetonide (7.7 min), olefin (12.6 min), epi-olefin (12.9 min)). The reaction was quenched by adding a cold solution of citric acid in THF (8.63 g in 60 mL THF). The resulting slurry was warmed to rt, concentrated to 450 mL volume and solvent switched to IPAC. To the resulting slurry was added 0.3 M H_2SO_4 (180 mL). Upon agitation and settling, the aqueous layer was cut and the organic layer was washed with water (180 mL) and 5% $NaHCO_3$ (180 mL). The organic layer was assayed by HPLC (Method D) to contain 55 g (98% yield) of olefin **4a**. The solution was used in the next step without further purification. A reference sample was prepared by passing this solution through a plug of silica, concentrating and crystallizing the residue from 3:1 MeOH/water. Mp = 79°C. $[\alpha]_D^{25} = +84$ (*c* 0.38, DCM). ^{1}H NMR (d_6 DMSO, 400 MHz) indicated a 6:1 mixture of rotamers: δ 7.30 (m, 5H), 7.01 (t, $J = 7$ Hz, 1H), 6.67 (dd, $J = 1$, 8 Hz, 1H), 6.35 (t, $J = 7$ Hz, 1H), 6.14 (d, $J = 7$ Hz, 1H), 5.95 (m, 1H), 5.24 (d, $J = 4$ Hz, 1H), 5.11 (m, 2H), 4.34 (m, 2H), 4.20 (m, 1H), 3.25 (m, 1H), 3.16 (m, 1H), 2.68 (dd, $J = 4$, 13 Hz, 1H), 2.33 (m, 2H), 1.55 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (d_6 DMSO, 100 MHz): δ 24.5, 26.9, 37.0, 38.8, 46.5, 52.2, 63.7, 70.5, 95.3, 116.6, 117.9, 121.0, 121.1, 126.8, 128.2, 128.7, 128.8, 129.6, 129.9, 135.6, 140.4, 153.0, 170.8. Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.28; H, 7.21; N, 3.68.

4.4. (2*S*,4*R*)-4-Benzyl-5-[(3a*S*,9b*S*)-2,2-dimethyl-3a,9b-dihydro-2*H*-chromeno[4,3-*d*]-[1,3]-oxazol-1(4*H*)-yl]-1-iodo-5-oxopentan-2-ol 5

To the solution of olefin (500 mL, 148 mmol) in IPAC was charged water (220 mL) and 5% $NaHCO_3$ (220 mL) and cooled to 3°C. *N*-Chlorosuccinimide (33.60 g, 252 mmol) was added followed by a 57% NaI solution (64.22 g, 244 mmol) over 40 min at 5°C. The resulting brown solution was allowed to warm to 20°C over 2 h and then was warmed to 30°C over 15 min and stirred for 4 h at this temperature [<0.1A% starting material remained as determined by HPLC (Method D)]. (Compound retention times: iodohydrin (9.3 min), olefin (12.6 min)). The reaction mixture was cooled to rt then quenched with 20% $Na_2S_2O_3$–$5H_2O$ (165 mL). The

aqueous layer was cut, and the organic layer was assayed by HPLC (Method D) to contain 64.0 g (84% yield) of iodohydrin **5**. This solution was used in the next step without further purification. A reference sample was prepared by drying this solution over anhydrous MgSO4, evaporating and crystallizing the residue from MeOH. Mp = 62–105°C. $[\alpha]_D^{25} = +59$ (*c* 0.29, DCM). ^{1}H NMR (d_6 DMSO, 400 MHz) indicated a 5:1 mixture of rotamers: δ 7.30 (m, 5H), 7.05 (~t, 1H), 6.70 (~d, 1H), 6.49 (~t, 1H), 6.35 (d, $J = 7$ Hz, 1H), 5.51 (br, 1H), 5.48 (d, $J = 4$ Hz, 1H), 4.38 (m, 2H), 4.20 (d, $J = 12$ Hz, 1H), 3.32 (m, 5H), 2.74 (m, 1H), 1.93 (m, 1H), 1.61 (s, 3H), 1.58 (m, 1H), 1.07 (m, 3H). ^{13}C NMR (d_6 DMSO, 100 MHz): δ 16.2, 24.6, 26.9, 38.7, 41.2, 43.4, 52.5, 63.8, 68.3, 70.6, 95.5, 116.8, 121.2, 121.3, 126.9, 128.2, 128.8, 128.9, 129.5, 129.8, 140.0, 153.1, 171.7. HRMS for $C_{24}H_{29}INO_4$ (M+H): 522.1136 (theory 522.1141).

4.5. (3a*S*,9b*S*)-1-{(2*R*)-2-Benzyl-3-[(2*S*)-oxiran-2-yl]propanoyl}-2,2-dimethyl-1,3a,4,9b-tetrahydro-2*H*-chromeno[4,3-*d*][1,3]oxazole 6

The solution of iodohydrin **5** in IPAC (520 mL, 148 mmol) was solvent switched to IPAC at <35°C and cooled to 15°C. Then 25% NaOMe (44.8 g, 207 mmol) in methanol was added and the mixture was stirred 1 h at 15°C. The reaction was determined complete (<0.2 A% starting material remained) by HPLC analysis (Method D). [Compound retention times: epoxide (8.0 min), iodohydrin (9.3 min)]. The reaction was quenched by adding water (170 mL) and the aqueous layer was quickly separated. The organic layer was washed with 10% Na_2SO_4–10H_2O (2×170 mL). The organic layer was concentrated and solvent switched to IPA at <45°C. The resulting slurry was heated rapidly to 80°C to dissolve all solids, cooled to 60°C to afford a thin slurry and was cooled further to 3°C over 4 h. The solids were filtered, rinsed with cold IPA (50 mL) and dried in a 40°C vacuum oven to afford 47.3 g (81% yield) of epoxide **6**. The ML loss was 2%. Mp = 129°C. $[\alpha]_D^{25} = +54$ (*c* 0.35, DCM). ^{1}H NMR (d_6 DMSO, 400 MHz) indicated a 4.7:1 mixture of rotamers: δ 7.32 (m, 5H), 7.03 (t, $J = 7$ Hz, 1H), 6.69 (d, $J = 7$ Hz, 1H), 6.40 (t, $J = 7$ Hz, 1H), 6.22 (d, $J = 7$ Hz, 1H), 5.33 (d, $J = 4$ Hz, 1H), 4.41 (m, 1H), 4.32 (m, 1H), 4.21 (d, $J = 12$ Hz, 1H), 3.34 (m, 1H), 3.24 (m, 1H), 3.09 (m, 1H), 2.79 (m, 2H), 2.49 (m, 1H), 1.74 (m 2H), 1.60 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (d_6 DMSO, 100 MHz): δ 24.2, 26.8, 37.2, 37.6, 44.9, 47.0, 49.9, 52.4, 63.7, 70.5, 95.3, 116.6, 121.0, 121.1, 126.9, 128.2, 128.8, 129.6, 129.9, 140.2, 153.0, 170.8. Anal. calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.13; H, 6.91; N, 3.50.

4.6. *N*-(2,2,2-Trifluoroethyl)pyrazine-2-carboxamide 9

Pyrazine 2-carboxylic acid (80.0 g, 644.6 mmol) was suspended in DMF (320 mL) and 2,2,2-trifluoroethylamine·HCl salt (79.8 g, 588.8 mmol), HOBt (4.0 g, 29.6 mmol), and TEA (68.0 g, 672.0 mmol) were sequentially added to the mixture with the temperature maintained below 35°C throughout the addition sequence. The mixture was cooled to 15°C and EDC·HCl (128.9 g, 672.4 mmol) was added portionwise over 1 h with the temperature maintained below 35°C. The reaction was aged at 25°C until <5% pyrazine 2-carboxylic acid remained (2–3 h; conversion determined by HPLC analysis (Method A)). (Compound retention times: pyrazine acid (2.10 min), pyrazine amide (12.66 min)). The reaction (off-white slurry) was diluted with 10% aqueous K_2CO_3 (1.60 L) with the temperature maintained below 35°C. The slurry was cooled to 10°C and aged for 2 h. The slurry was filtered to collect the solids and the filter-cake was washed with DI water (800 mL). The solids were dried under a nitrogen atmosphere at 40°C and 23″ Hg until >80% dry. Yield: 106.3 g of pyrazine amide (>99 A%; 98.4 wt%; 86% corrected yield; 12% loss to ML's and wash). Mp 119–120°C; IR (thin film) 3351, 1677, 1668, 1526, 1259, 1225, 1148, 1037, 1023, 668, 503 cm^{-1}; ^{1}H NMR: (CD_3CN, 400 MHz): $\delta = 9.28$ (d, $J = 1.5$ Hz, 1H), 8.80 (d, $J = 2.5$ Hz, 1H), 8.61 (dd, $J = 2.6$, 1.5 Hz, 1H), 8.40 (bs, 1H), 4.14 (dq, $J = 9.4$, 6.8 Hz, 2H); ^{13}C NMR (CD_3CN, 100 MHz): $\delta = 164.8$, 149.0, 145.0, 144.7, 144.2, 125.6 (q, $J = 278.2$ Hz), 41.0 (q, $J = 34.7$ Hz); HRMS (ESI): m/z 206.0538 ([M+H]$^+$, $C_7H_7F_3N_3O$, calcd 206.0541).

4.7. Racemic *N*-(2,2,2-trifluoroethyl)piperazine-2-carboxamide 11

A heterogeneous mixture of *N*-(2,2,2-trifluoroethyl)-pyrazine-2-carboxamide (106.3 g, 518.2 mmol), 20% $Pd(OH)_2/C$ (20.9 g, 20 wt% charge) and punctilious ethanol (1.05 L) was aged for 1–2 h at 10 to 15°C under 5 psig hydrogen. The hydrogen pressure was increased to 40 psig while maintaining the reaction temperature between 58 and 62°C. After 8 h at 60°C, the reaction was >99% complete as determined by HPLC analysis (Method B). (Compound retention times: piperazine amide (2.17 min), pyrazine amide (6.07 min)). The reaction temperature was adjusted to 25°C and the catalyst was removed via filtration through solka floc. The reaction vessel was rinsed with punctilious ethanol (720 mL) and used to wash the filter-cake. The ethanol solutions were combined and assayed by HPLC (Method B: 104.16 g of racemic piperazine amide (97% yield)). The ethanol solution was taken forward to the resolution step without further modification. A reference sample was isolated by flash chromatography (5:40:55 MeOH:EtOAc:DCM) for characterization purposes. Mp 142–145°C; IR (thin film) 3294, 2936, 2815, 1672, 1559, 1521, 1212, 1154, 832, 503 cm^{-1}; ^{1}H NMR (CD_3CN, 400 MHz): δ 7.58 (bs, 1H), 3.90 (dq, $J =$ 9.5,6.7 Hz, 2H), 3.24 (dd, $J = 7.9$, 5.5 Hz, 1H), 2.96 (dd, $J = 12.1$, 3.6 Hz, 1H), 2.84–2.78 (m, 1H), 2.77-2.67 (m, 3H), 2.66–2.56 (m, 1H), 1.90 (s, 2 H); ^{13}C NMR (CD_3CN, 100 MHz): $\delta = 174.0$, 125.7 (q, $J = 278.3$ Hz), 59.6, 49.7, 47.1, 45.8, 40.5 (q, $J = 34.1$ Hz); HRMS (ESI): m/z 212.1016 ([M+H]$^+$, $C_7H_{13}F_3N_3O$, calcd 212.1011).

4.8. (2*S*)-*N*-(2,2,2-Trifluoroethyl)piperazine-2-carboxamide bis-(1*S*)-(+)-10-camphor-sulfonic acid salt, monohydrate 11·2CSA

The ethanol solution of racemic piperazine amide (98.6

g, 467.0 mmol) was concentrated under vacuum (internal temperature maintained between 14 and 20°C) to a total volume of 390 mL. Acetonitrile (800 mL) was added to the slurry that formed upon distillation to dissolve the solid. In a separate vessel, (1*S*)-(+)-10-camphorsulfonic acid (184.4 g, 793.9 mmol) was dissolved in acetonitrile (1.80 L). Upon complete dissolution of the solid, the (*S*)-CSA/CH_3CN solution was transferred to the piperazine amide/CH_3CN/EtOH solution. Water (104 g) was added to the salt mixture to give a total water content of 0.13 equiv. versus piperazine amide. The mixture was heated to 73°C to dissolve any solids. After dissolution of solids, the solution was cooled to 62°C and seeded with pip-amide-bis-(*S*)-CSA salt (0.1 wt%, 0.1 g) as a slurry in acetonitrile (2.0 mL). After aging the seed bed for 2 h at 62°C, the heating was discontinued and the slurry was cooled to rt over 12–18 h. The slurry was filtered to collect the solids and the filter-cake washed with 26:2.9:1.1 (v:v:v) CH_3CN:EtOH:H_2O, (2×300 mL). The filter-cake was dried under a nitrogen atmosphere at 40°C and 22″ Hg to a constant weight. A total of 102.0 g (31.5% yield) of the desired bis (*S*)-CSA (*S*)-piperazine amide salt, monohydrate was obtained with an ee of 98.6% as determined by HPLC analysis (Method C). (Assay Sample Prep: Slurried 30 mg of pip amide salt in CH_2Cl_2 (1.0 mL) and added triethylamine (25 μL) to give a homogenous solution. BOC_2O (15 mg) was added and the solution stirred. The solvent was removed under a stream of nitrogen and the residue was dissolved in methanol (1.0 mL). The methanol solution was used for the chiral assay.) Compound retention times: (*S*)-CSA (0.98 min), (*S*)-BOC piperazine amide (2.27 min), (*R*)-BOC piperazine amide (3.43 min), Bis-BOC piperazine amide (7.45 min)). Mp 238–240°C; $[\alpha]_D^{25} = +31.1$ (*c* 1, methanol); IR (thin film) 2960, 1743, 1707, 1573, 1557, 1454, 1206, 1152, 1040, 503 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz): δ 4.84 (bs, 5H), 4.64 (dd, $J = 12.0$, 3.6 Hz, 1H), 4.13–3.94 (m, 3H), 3.77 (m, 2H), 3.66 (m, 1H), 3.54–3.43 (m, 2H), 3.28 (d, $J = 14.7$ Hz, 2H), 2.82 (d, 14.7 Hz, 2H), 2.55 (m, 2H), 2.36 (m, 2H), 2.12–1.998 (m, 4H), 1.92 (d, $J = 18.4$ Hz, 2H), 1.72 (m, 2H), 1.45 (m, 2H), 1.09 (s, 6H), 0.87 (s, 6H); ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 218.9$, 166.3, 125.5 (q, $J = 277.8$ Hz), 59.6, 55.0, 49.1, 48.6, 44.0, 43.9, 43.7, 41.6 (q, $J = 34.9$ Hz), 41.3, 41.1, 27.8, 25.9, 20.1, 20.0. Anal. calcd for $C_{27}H_{46}F_3N_3O_{10}S_2$: C, 46.74; H, 6.68; F, 8.22; N, 6.06; O, 23.06; S, 9.24. Found: C, 46.83; H, 6.62; F, 8.27; N, 5.96; O, 23.14; S, 9.18.

4.9. *tert*-Butyl-(2*S*)-2-{[(2,2,2-trifluoroethyl)amino]-carbonyl}-piperazine-1-carboxylate 12

Bis (*S*)-CSA piperazine amide salt (45.0 g, 64.9 mmol) was suspended in a mixture of isopropyl acetate (256 mL) and acetonitrile (128 mL). Triethylamine (13.2 g, 130.4 mmol) and water (5.4 g, 1.25 vol.%) were added and the mixture was agitated at 15 to 25 until homogenous (1 h). (Note: If triethylamine is undercharged relative to the CSA (<1:1), significantly higher amounts of the bis-BOC impurity will be formed.) A solution of di-*tert*-butyl dicarbonate (14.2 g dissolved in 2:1 v/v IPAc:MeCN (67.5 mL)) was then added over 30 min. The reaction was aged for 2 h and determined complete (<5% starting material remained) by HPLC analysis (Method B). (Compound retention times: piperazine amide (1.9 min), CSA (7.5 min), BOC piperazine amide (8.4 min), bis-BOC piperazine amide (19.2 min)). Water (225 mL) was added to the reaction, followed by IPAc (300 mL). The mixture was agitated and the layers were separated upon settling. The organic layer was concentrated under vacuum to ~50 mL. IPA (318 mL) was added in two equal portions, concentrating under vacuum to ~60 mL after each addition. The final solution contained 17.8 g (88% yield) of **12** as determined by HPLC (Method B) and was taken forward without further modification. A reference sample was isolated by flash chromatography (40% EtOAc/60% DCM) as a thick clear oil for characterization purposes. $[\alpha]_D^{25} = +20.2$ (*c* = 1, methanol); IR: 3308, 2978, 2863, 1685, 1522, 1425, 1367, 1271, 1162, 992, 864, 665; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.39$ (app t, $J = 6.3$ Hz, 1H), 3.96 (dd, $J = 3.5$, 13.4 Hz, 1H), 3.88 (m, 2H), 3.67 (d, $J = 11.5$ Hz, 1H), 3.39 (dd, $J = 3.8$, 8.6 Hz, 1H), 3.13 (dd, $J = 8.6$, 13.3 Hz, 1H), 3.02 (br, 1H), 2.91 (m, 1H), 2.77 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 171.4$, 154.4, 123.9 (q, $J = 278.5$ Hz), 80.2, 57.7, 45.6 (br), 44.0 (br), 43.6, 40.2 (q, $J = 34.7$ Hz), 28.2; HRMS (ESI): *m*/*z* 623.2988 ($[2M+H]^+$, $C_{24}H_{41}F_6N_6O_6$, calcd 623.2992); 334.1382 ($[M+Na]^+$, $C_{12}H_{20}F_3N_3O_3Na$, calcd 334.1354.

4.10. *tert*-Butyl (3*S*)-4-{(2*S*,4*R*)-4-benzyl-5-[(3a*S*,9b*S*)-2,2-dimethyl-3a,9b-dihydro-2*H*-chromeno[4,3-*d*][1,3]-oxazol-1(4*H*)-yl]-2-hydroxy-5-oxopentyl}-3-{[(2,2,2-trifluoro-ethyl)amino]carbonyl}piperazine-1-carboxylate 13

Epoxide (82.3 g, 209 mmol) was added to a 2 L flask to a solution of BOC-piperazine amide in IPA (34.2 wt%, 200 g, 220 mmol). The slurry was heated to reflux at 90°C under N_2. The solution was stirred 64 h at 90°C after which the reaction was complete (<0.1A% epoxide) as determined by HPLC (Method E). (Compound retention times: BOC-piperazine amide (5.8 min), coupled product (10.6 min), epoxide (11.6 min)). This solution was used in the next reaction. A reference sample was prepared by concentrating this solution and purifying the residue by flash chromatography (70% EtOAc/hexane) to afford a white solid. Mp = 106–124°C. $[\alpha]_D^{25} = +44$ (*c* 0.29, DCM). ^1H NMR (d_6 DMSO, 400 MHz) indicated a 7:1 mixture of rotamers: δ 8.67 (t, $J = 6$ Hz, 1H), 7.29 (m, 5H), 7.01 (t, $J = 8$ Hz, 1H), 6.68 (d, $J = 8$ Hz, 1H), 6.42 (t, $J = 7$ Hz, 1H), 6.27 (d, $J = 7$ Hz, 1H), 5.60 (d, $J = 4$ Hz, 1H), 4.86 (d, $J = 4$ Hz, 1H), 4.36 (m, 2H), 4.20 (d, $J = 12$ Hz, 1H), 3.95 (m, 1H), 3.84 (m, 1H), 3.65 (br, 1H), 3.50 (br, 2H), 3.22 (m, 1H), 2.97 (m, 3H), 2.74 (dd, $J = 5$, 13 Hz, 1H), 2.38 (m, 1H), 2.21 (m, 2H), 1.88 (m, 1H), 1.58 (s, 3H), 1.38 (m, 1H), 1.36 (s, 9H), 1.07 (s, 3H). ^{13}C NMR (d_6 DMSO, 100 MHz): δ 24.3, 26.9, 28.3, 38.4, 43.9, 52.3, 62.6, 63.8, 65.4, 70.7, 79.4, 95.2, 116.7, 121.2, 121.2, 126.8, 128.2, 128.8, 129.8, 140.4, 153.0, 153.9, 171.6, 171.9. HRMS for $C_{36}H_{48}F_3N_4O_7$ (M+H): 705.3466 (theory 705.3475).

4.11. (2*S*)-1-((2*S*,4*R*)-4-Benzyl-5-{[(3*S*,4*S*)-3-hydroxy-3,4-dihydro-2*H*-chromen-4-yl]amino}-2-hydroxy-5-oxopentyl)-*N*-(2,2,2-trifluoroethyl)piperazine-2-carboxamide 14

The coupling reaction mixture was cooled to −8°C and conc HCl (470 mL) was added over 33 min at <8°C. CO_2 and isobutylene gas are liberated during this addition. The resulting solution was stirred at 6°C for 4 h until reaction was complete as determined by HPLC (Method E). (Compound retention times: penultimate (6.7 min)). The solution was cooled to −10°C and 22 wt% NaOH (927 g) was added over 1 h to adjust the pH of the solution to 10.4. IPAC (470 mL) was added and the mixture was warmed to 21°C to dissolve solids that had formed and more 22 wt% NaOH (50 g) was added to adjust to pH 10.0. The aqueous layer was cut and the organic layer was washed with water (150 mL) at 50°C. The solvent was switched to IPAC via distillation and adjusted to 1.33 L volume. The solution was heated to 70°C, seeded (1 g 14), and cooled to 50°C over 2 h and stirred 4 h to afford a slurry. *n*-Heptane (1.33 L) was added at 50°C over 4 h and was cooled slowly to rt. The solids were filtered, rinsed with 1:1 IPAC/*n*-heptane (1 L) and dried in a 40°C vacuum oven to afford 99.1 g (84% yield) of penultimate 14. The loss to the ML and rinse was 3%. Mp = 146°C. $[\alpha]_D^{25} = +38$ (*c* 0.39, DCM). ^{1}H NMR (d_6 DMSO, 400 MHz): δ 8.38 (t, $J = 6$ Hz, 1H), 7.80 (d, $J = 9$ Hz, 1H), 7.23 (m, 5H), 7.08 (m, 2H), 6.78 (∼t, 1H), 6.70 (∼d, 1H), 5.10 (m, 2H), 4.55 (d, $J = 4$ Hz, 1H), 4.13 (d, $J = 11$ Hz, 1H), 4.06 (dd, $J = 4$, 12 Hz, 1H), 3.93 (m, 1H), 3.78 (m, 1H), 3.73 (m, 2H), 2.95 (m, 2H), 2.6–2.9 (m, 7H), 1.9-2.3 (m, 5H), 1.16 (m, 1H). ^{13}C NMR (d_6 DMSO, 100 MHz): δ 38.0, 39.5, 44.2, 45.1, 47.2, 48.7, 51.7, 63.0, 63.7, 65.6, 66.9, 68.7, 115.9, 120.3, 122.8, 126.2, 128.4, 128.8, 129.3, 140.3, 154.3, 172.7, 175.5. Anal. calcd for $C_{28}H_{35}F_3N_4O_5$: C, 59.56; H, 6.25; N, 9.92. Found: C, 59.25; H, 6.24; N, 9.70.

4.12. 5-(5-Chloropyridin-2-yl)-2-furaldehyde 16

2-Furaldehyde diethyl acetal (20.0 g, 117.5 mmol) was charged to a vessel containing THF (100 mL) and TMEDA (15.1 g, 129.5 mmol). The solution was cooled to −40°C and 1.6 M *n*-BuLi (84.4 mL, 135.1 mmol) was added over 1 h with the temperature maintained below −20°C. The solution was aged for 15 min at −25°C and determined complete (<5% 2-furaldehyde remained) by HPLC analysis (Method F). ((Assay Sample Prep—5-methyl-2-furaldehye: Cold reaction mixture (0.50 mL; *T* <−20°C) was quenched into cold MeI (0.50 mL; *T* <−20°C). Dilute an aliquot to approximately 10 mL using 50:50 ACN: aqueous 0.1 M H_3PO_4). Compound retention times: 2-furaldehyde (1.54 min), 5-methyl-2-furaldehye (2.07 min).

A $ZnCl_2$/THF slurry was prepared by adding solid $ZnCl_2$ (11.2 g) to THF (50 mL). The slurry was azeotropically dried by the distillation of THF until an acceptable water concentration was obtained (KF <750 ppm). The furyl-Li solution was cooled to −35°C and the $ZnCl_2$/THF slurry (11.2 g, 82.3 mmol) was added over 1 h with the temperature maintained <−20°C throughout the addition. The reaction was aged for 30 min at −25°C and warmed to 25°C over 1 h. $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.48 g, 0.59 mmol) and 2,5-dichloropyridine (19.2 g, 129.5 mmol) were charged at 23°C. The reaction was heated to 55°C, aged for 3 h, and determined complete by HPLC analysis (Method F). (Compound retention times: 2-furaldehyde (1.54 min), 2,5-dichloropyidine (6.13 min), biaryl aldehyde product (7.66 min)). The reaction mixture was cooled to 0°C and quenched with chilled 5N HOAc (117.5 mL, 592.8 mmol). The aqueous phase was cut and the organic phase was washed with 10% NaOH (100 mL) followed by saturated brine (50 mL).

The organic solution was concentrated under vacuum to approximately 100 mL and a constant volume solvent switch was performed: *n*-Heptane was continuously added to the THF solution of biaryl acetal with the volume maintained at approximately 100 mL (T maintained <40°C, 20 to 28″ Hg). After distilling through ∼400 mL of heptane, <1% THF remained. The heptane solution of biaryl acetal was transferred to a vessel containing Darco G-60 (10.0 g). The mixture was heated up to 50°C and aged for 2 h at 50°C. The mixture was then cooled to 23°C over 1 h, and aged for 15 h at 23°C. The slurry was filtered through a bed of solka floc and the filter-cake was washed with heptane (200 mL). The combined filtrate and wash solution assayed at 16.6 g (68% yield) by HPLC (Method F).

Deprotection and crystallization of **16**: The heptane solution of biaryl acetal was concentrated to 270 mL (20 to 28″ Hg., temp. maintained <40°C) and THF (20 mL) was added. 5 M HCl (2.5 mL, 11.75 mmol) was diluted into THF (10 mL) and 25% of this solution was added to the solution of the acetal. The mixture was seeded with pure product (0.20 g, 1 wt%) and aged for 15 min at 25°C. The remainder of the HCl/THF solution was added to the slurry over 15–20 min with the temperature maintained at ∼25°C. The resulting slurry was distilled at constant volume to remove THF and EtOH by the addition of heptane. The slurry was aged for 30 min at 25°C, filtered to collect the product, and the filter-cake was washed with heptane (200 mL). The aldehyde was dried to a constant weight under a nitrogen atmosphere at 40°C and 23″ Hg. Isolated 16.58 g of biaryl aldehyde (93.6 wt.%, 63.6% corrected yield; 3.3% loss to ML's and wash) as a tan solid (>98 A% purity by HPLC Method F).

4.13. (2*S*)-1-((2*S*,4*R*)-4-Benzyl-5-{[(3*S*,4*S*)-3-hydroxy-3,4-dihydro-2*H*-chromen-4-yl]-amino}-2-hydroxy-5-oxopentyl)-4-{[5-(5-chloropyridin-2-yl)-2-furyl]methyl}-*N*-(2,2,2-trifluoroethyl)piperazine-2-carboxamide 1

DMF (120 mL), penultimate **14** (15.0 g, 26.57 mmol) and aldehyde **16** (6.07 g, 29.22 mmol) were charged to a vessel under nitrogen. The resulting solution was aged at 20–25°C for 15 min and then cooled to 0–2°C. HOAc (7.60 mL, 132.8 mmol) was added over 15 min

while maintaining temperature <5°C. The solution was cooled to 0°C and $NaBH(OAc)_3$ (6.19 g, 29.22 mmol) was added in one portion. The mixture was aged 15 min at 0–5°C and then warmed to 20–25°C over 0.5–1 h. The resulting solution was aged at 20–25°C for 3 h and assayed by HPLC (Method G). [Compound retention times: penultimate (6.5 min), aldehyde (9.1 min), bicyclic aminal **18** (19.2 min), free base **1** (23.0 min)]. Upon completion of the reaction (<2 A% penultimate remains), H_2O (30 mL) was added. The solution was warmed to 50°C and seeded with pure free base (1 wt%). The thin slurry was aged 0.5 h at 50°C and H_2O (270 mL) was added over 30 min. The resulting thick slurry was aged 1 h at 50°C and then filtered. The filter-cake was washed with H_2O (150 mL) and dried under N_2 for 4–6 h. The filter-cake was further dried to a constant weight in a vacuum oven (60°C, 23″ Hg). Isolated 19.2 g (96.2 wt%, 91.6% yield, <1.5% loss to ML's and wash) of an off-white crystalline solid.

MeOH (425 mL) and crude free base **1** (12.98 g, 17.16 mmol) were charged to a vessel and the resulting slurry was warmed to 60–64°C. Darco G-60 (2.6 g) was charged to the hot MeOH solution and aged 1 h at 55°C. The hot slurry was filtered through solka floc and the filter-cake was washed with MeOH (142 mL). The filtrate was concentrated to a total volume of 284 mL (18–20°C, 80–85 torr) and the resulting slurry was warmed to 60–64°C to dissolve all solids. The batch was seeded with pure free base (1.0 wt%) at 58°C, aged at 55–58°C for 0.5 h, and then slowly cooled to 20–23°C over 1 h. The slurry was solvent switched to *n*-PrOH by constant volume distillation (distillation complete when <5% MeOH remained; final volume: 210 mL). The slurry was filtered at 20–25°C and dried to a constant weight in a vacuum oven (60°C, 23″ Hg). Isolated 11.2 g and analyzed by HPLC (Method G, >99.4 A%, >99 wt.%, 86% yield from crude **1**, 6–8% loss to ML's and wash). Mp 203–204°C; $[\alpha]_D^{25} = +20.0$ ($c = 1$, 0.01N HCl/methanol); IR: 3304, 2958, 2820, 1658, 1212, 1152, 1018, 798, 638, 499 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 400 MHz): $\delta = 8.60$ (d, $J = 2.4$ Hz, 1H), 8.43 (t, $J = 6.5$ Hz, 1H), 7.95 (dd, $J = 2.4$, 8.7 Hz, 1H), 7.81 (d, $J = 8.8$ Hz, 1H), 7.70 (d, $J = 8.6$ Hz, 1H), 7.27–7.20 (m, 4H), 7.18–7.14 (m, 1H), 7.10–7.00 (m, 3H), 6.78 (t, $J = 7.4$ Hz, 1H), 6.71 (d, $J = 8.3$ Hz, 1H), 6.50 (d, $J = 3.3$ Hz, 1H), 5.12 (dd, $J = 3.8$, 8.9 Hz, 1H), 5.09 (d, $J = 3.6$ Hz, 1H), 4.59 (d, $J = 4.3$ Hz, 1H), 4.16–4.00 (m, 2H), 3.95–3.86 (m, 1H), 3.84–3.76 (m, 1H), 3.75–3.73 (m, 1H), 3.67 (bs, 1H), 3.62 (s, 2H), 3.05–2.90 (m, 4H), 2.70–2.58 (m, 3H), 2.43 (t, $J = 9.6$ Hz, 1H), 2.37–2.18 (m, 4H), 1.98 (t, $J = 11.5$, 1H), 1.17 (t, $J = 10.8$ Hz, 1H); ^{13}C NMR ($(CD_3)_2SO$): $\delta = 175.1$, 171.7, 153.9, 153.2, 151.5, 148.1, 147.0, 139.9, 136.8, 128.9, 128.4, 128.0, 126.0, 125.8, 122.4, 119.9, 119.3, 115.5, 111.6, 110.3, 68.3, 65.5, 63.3, 61.6, 53.7, 51.1, 50.3, 46.8, 43.8, 37.5; HRMS (ESI): m/z 756.2781 ($[M+H]^+$, $C_{38}H_{42}ClF_3N_5O_6$, calcd 756.2776).

4.14. (2*R*,4*S*)-2-Benzyl-5-[(5*S*)-2-[5-(5-chloropyridin-2-yl)-2-furyl]-4-oxo-3-(2,2,2-trifluoroethyl)-1,3,6-triazabicyclo[3.3.1]non-6-yl]-*N*-[(3*S*,4*S*)-3-hydroxy-3,4-dihydro-2*H*-chromen-4-yl]-4-hydroxypentanamide 18

To a solution of penultimate **14** (0.565 g, 1.0 mmol) and aldehyde **16** (0.228 g, 1.1 mmol) in DMF-d_7 (2.3 mL) was added HOAc (0.29 mL, 5.0 mmol). The solution was aged at 23°C for 48 h. Compound **18** formed in ~60% conversion. ^1H NMR (600 MHz, DMF-d_7-selected data) δ 7.16 (d, $J = 3.4$ Hz, 1H), 6.60 (d, $J = 3.4$ Hz, 1H), 5.70 (s, 1H), 4.95 (dq, $J = 15.5$, 9.4 Hz, 1H), 3.57 (dq, $J = 15.5$, 9.4, 1H); ^{13}C NMR (150 MHz, DMF-d_7) δ 175.9, 166.4, 154.6, 152.9, 152.6, 148.6, 147.3, 140.5, 137.1, 130.0, 129.2, 129.0, 128.3 (2C), 126.2, 125.4 (q, $J = 280.8$ Hz), 122.7, 120.4, 119.7, 115.9, 111.6, 110.2, 75.1, 68.8, 65.5, 64.4, 63.1, 57.2, 53.1, 47.7, 47.0, 46.8, 45.0, 42.9 (q, $J = 42.9$ Hz), 39.6, 37.8.

4.15. (2*S*)-1-((2*S*,4*R*)-4-Benzyl-5-{[(3*S*,4*S*)-3-hydroxy-3,4-dihydro-2*H*-chromen-4-yl]-amino}-2-hydroxy-5-oxopentyl)-4-{[5-(5-chloropyridin-2-yl)-2-furyl]methyl}-*N*-(2,2,2-trifluoroethyl)piperazine-2-carboxamide bisbenzenesulfonic acid salt 1·2BSA

A solution of 0.1 g/mL benzene sulfonic acid in EtOH (31.4 mL, 19.83 mmol, KF<800 ug/mL) was added to a 23°C slurry of free base **1** (10.0 g, 13.22 mmol) in EtOH (36 mL). The resulting slurry was warmed to 50°C and the resulting solution was then seeded with crystalline **1** bis besylate salt (70 mg, 0.5 wt%). Additional benzene sulfonic acid in EtOH (13.0 mL, 7.93 mmol, 2.1 equiv. total) was added over 1 h while maintaining the slurry at 50°C. The thick slurry was aged 0.5 h at 50°C, 1 h at 23°C and then filtered. The filter-cake was washed with EtOH (30 mL). The solid was dried in a vacuum oven at 40°C (23″Hg, 31 h). Isolated 11.9 g (HPLC Method G, >98.5 A%, 84% yield) of a white crystalline solid. Mp 139–142°C (decomposed); $[\alpha]_D^{25} = +15.9$ (c 1, methanol); IR: 3298, 3061, 1700, 1653, 1636, 1540, 1213, 1154, 1016, 729, 612, 503 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 400 MHz): $\delta = 9.39$ (bs, 1H), 8.64 (d, $J = 2.5$, 1H), 8.00 (ddd, $J = 0.7$, 2.4, 8.6 Hz, 1H), 7.94 (d, $J = 8.9$ Hz, 1H), 7.76 (d, $J = 8.5$ Hz, 1H), 7.66–7.60 (m, 4H), 7.37–7.30 (m, 6H), 7.29–7.16 (m, 7H), 7.14–7.00 (m, 2H), 6.81 (t, $J = 7.5$ Hz, 1H), 6.76 (d, $J = 3.2$ Hz, 1H), 6.71 (d, $J = 8.2$ Hz, 1H), 7.00–5.80 (broad, 2H), 5.14 (dd, $J = 3.7$, 8.8 Hz, 1H), 4.21–3.90 (m, 9H), 3.76 (s, 1H), 3.69 (bs, 1H), 3.44 (d, $J = 11.2$ Hz, 1H), 3.30 (d, $J = 11.1$ Hz, 1H), 3.20 (t, $J = 11.2$ Hz, 1H), 3.05–2.90 (m, 6H), 2.63 (m, 1H), 1.74 (t, $J = 10.8$ Hz, 1H), 1.31 (t, $J = 11.6$ Hz, 1H); ^{13}C NMR ($(CD_3)_2SO$): $\delta = 174.5$, 166.6, 154.1, 153.1, 148.3, 147.7, 146.6, 139.6, 137.1, 129.7, 129.0, 128.9, 128.8, 128.2, 128.1, 127.9, 126.1, 125.9, 125.6, 123.1, 122.3, 120.3, 120.0, 115.6, 110.7, 68.5, 65.0, 63.3, 59.9, 51.7, 48.0, 46.9, 43.2, 37.4. Anal. calcd for $C_{50}H_{53}ClF_3N_5O_{12}S_2$: C, 55.99; H, 4.98; Cl, 3.31; F, 5.31; N, 6.53; O, 17.90; S, 5.98. Found: C, 55.88; H, 4.94; Cl, 3.31; F, 5.35; N, 6.55; O, 17.95; S, 6.02.

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