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# Multigram Preparation of BRD4780 Enantiomers and Assignment of Absolute Stereochemistry

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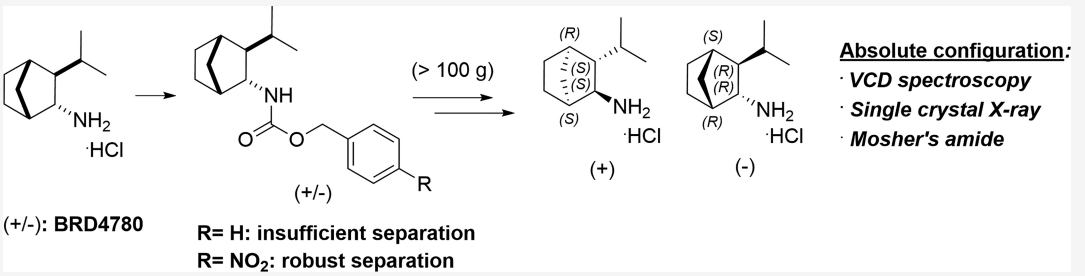


**ABSTRACT:** The development of a multigram synthesis of 3-*exo*-isopropylbicyclo[2.2.1]heptan-2-*endo*-amine hydrochloride (**1**) (also known as BRD4780 and AGN-192403) is described. The process involves protection of the amine as 4-nitrobenzyl carbamate, pNZ, which enables chiral SFC chromatography. The absolute configuration (AC) of the individual enantiomers has been determined by Mosher's amide method, VCD spectroscopy, and X-ray crystallography. We highlight the VCD approach as a rapid and effective means of AC determination that can be deployed directly on the target compounds.



BRD4780 (AGN-192403, *rac*-3-*exo*-isopropybicyclo[2.2.1]-heptan-2-*endo*-amine hydrochloride, (±)-**1**) was first reported as a selective imidazoline **1** receptor ligand by Munk and co-workers in 1996.[1] BRD4780 is contained within the Broad Institute's Drug Repurposing Hub, which contains ∼7000 small molecules spanning different phases of preclinical and clinical development.[2] A high-content screen (HCS) identified (±)-**1** as a compound that clears a mutant, misfolded version of the surface glycoprotein Mucin 1 (MUC1) (called frameshift MUC1 or MUC1-fs) from the early secretory compartment of kidney epithelial cells. The screen was performed in a human immortalized kidney tubular epithelial cell line derived from a MUC1 kidney disease (MKD) patient. Treatment with (±)-**1** removed MUC1-fs from these cells, while leaving wild-type MUC1 unaffected.[3] These results were extended to human kidney organoids and an *in vivo* mouse model of MKD.[3] Compound (±)-**1** is able to exert similar effects in other toxic proteinopathies in which there is misfolded protein accumulation in the early secretory compartments.[3] We have developed an approach to preparing the individual enantiomers of **1** based on chiral SFC, have demonstrated these methods as effective on a multigram scale, and have assigned the absolute configurations (AC) of the compounds. The individual enantiomers of the minor *exo* product generated from the Diels−Alder reaction of (*E*)-3-methyl-1-nitrobut-1-ene, **3**, and cyclopentadiene were also isolated and the ACs determined. The preparation of these compounds on a multigram scale could enable a more nuanced study of the pharmacology of these and related compounds, both *in vitro* and *in vivo*.

We first examined the potential for direct resolution of (±)-**1** across a series of chiral SFC columns in a range of solvent systems as monitored by MS detection and did not observe separation (stationary and mobile phases are provided in the Experimental Section). Next, we attempted to isolate the individual enantiomers of the *rac*-3-*exo*-isopropyl-2-*endo*-nitrobicyclo[2.2.1]hept-5-ene products, **12**, generated from the Diels−Alder reaction of **3** and cyclopentadiene (Scheme 1). As reported by Munk and co-workers,[1] isolation of pure **12** is challenging, and we, therefore, profiled the separation of the mixture of **12** and the undesired *rac*-3-*endo*-isopropyl-2-*exo*-nitrobicyclo[2.2.1]hept-5-ene, **13**, as a crude mixture. No separation was observed across the stationary phases, except with the AD-H column, which did not present sufficient dispersion of the 4 peaks. Given these results, we pursued a strategy in which a UV−visible protecting group was incorporated on the primary amine of (±)-**1** to facilitate separation and detection.

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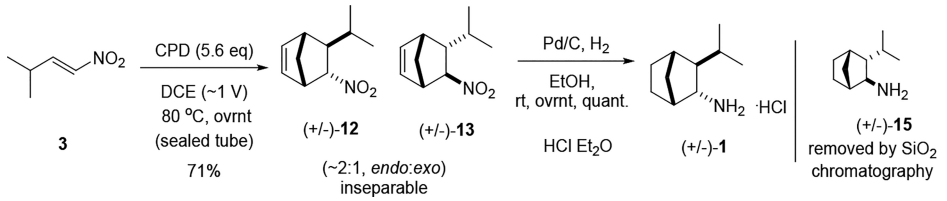
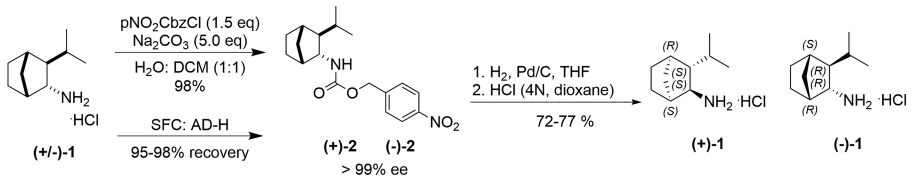
**Scheme 1. Literature Synthesis of (±)-1**




**Scheme 2. Synthesis and Separation of Each Enantiomer, (+)-1 and (−)-1, from (±)-1**




We first examined CBz due to its ease of incorporation and removal ((±)-**4**). Although separation of the enantiomers of (±)-**4** was observed with the OJ-H column, we were disappointed to discover that the separation efficiency was insufficient to support semipreparative scale separations. Peak overlap and tailing resulted in poor material recovery on the semipreparative scale: (+)-**4**, fraction 1 = 62% theoretical yield, (−)-**4**, fraction 2, = 80% theoretical yield, and only 90% ee for (−)-**4**. On the basis of these results, we concluded that the Cbz protection strategy was not viable for the preparation of (+)-**1** and (−)-**1**.

In order to discover a suitable auxiliary, we prepared *N*-protected derivatives of (±)-**1** that encompassed a range of functional groups and deprotection methodologies ((±)-**2**, 4-nitrobenzyl carbamate, pNZ; (±)-**4**, Cbz; (±)-**5**, 4-bromobenzyl carbamate; (±)-**6**, FMOC; (±)-**7**, tosyl; (±)-**8**, *o*-nosyl; (±)-**9**, *N*-dibenzyl; (±)-**10**, phthalimido; and an acetamide, (±)-**11**, prepared from *rac*-3-*exo*-isopropylbicyclo[2.2.1]hept-5-en-2-*endo*-amine). A description of the separation efficiencies of these compounds is reported in the Supporting Information. Briefly, the *N*-tosyl derivative, (±)-**7**, and the pNZ compound, (±)-**2**, showed the best separation using the AD-H column. Optimization of the solvent system and gradient provided robust separation of (±)-**7** ($\Delta t_R$ = 0.78 min) and (±)-**2** ($\Delta t_R$ = 0.46 min). For comparison, moderate separation of the Cbz, (±)-**4** ($\Delta t_R$ = 0.14 min), and 4-bromobenzyl carbamate, (±)-**5** ($\Delta t_R$ = 0.21 min), analogues were observed on the OD-H column, following method optimization.

We explored the potential to deprotect (±)-**7** and (±)-**2** in order to regenerate (±)-**1**. While the pNZ group of (±)-**2** was easily removed by catalytic hydrogenation, removal of the tosyl group of (±)-**7** could not be achieved by the reaction of *in situ* generated trimethylsilyl iodide (TMSI)[4] or by reaction with sodium metal in refluxing isopropanol.[5] Accordingly, we attempted the separation of the pNZ-protected (±)-**2** and were able to achieve clean enantiomer separation with high recovery on the semipreparative scale. Full baseline separation of 25 mg injections was observed on a Chiralpak AD-H column (250 mm × 21 mm, 5 μm, 90 g/min, 0−10% IPA gradient) and with high recovery ((+)-**2**, fraction 1 = 88% theoretical yield; (−)-**2**, fraction 2 = 91% theoretical yield). Analytical chiral SFC analysis demonstrated trace absorption at the retention time of the other enantiomer (>99% ee). Given these results, we scaled the process and generated 120 g of (±)-**2** (4-nitrobenzyl chloroformate, $Na_2CO_3$ in water/DCM at rt; 98.0% yield). Again, we observed full baseline separation with up to 500 mg injections on a Chiralpak AD-H column (250 mm × 25 mm, 10 μm, flow rate = 70 g/min, 0−35% IPA gradient) and achieved excellent recovery of >99% ee material ((+)-**2** = 58 g (97% recovery), 99.7% ee, $[\alpha]_D^{24}$ +21.8 (*c* 0.72, $CH_3CN$); (−)-**2** = 57 g (95% recovery), 99.8% ee, $[\alpha]_D^{25}$ −20.5 (*c* 1.16, $CH_3CN$). The injection cycle time was 8 min, and we were able to separate ∼50 g of racemic material in less than a day of instrument time at a flow rate of 70 g/min.

Deprotection of the pNZ group at scale by catalytic hydrogenation using 10% Pd/C in THF under an atmosphere of $H_2$ proceeded well to generate a mixture of the free base of (+)-**1** or (−)-**1** and *p*-toluidine.[6] *p*-Toluidine is separated from the desired product using normal phase silica gel chromatography with the full deprotection sequence being accomplished in 72−77% yields. The analytical characterization of the products was identical with authentic BRD4780/AGN-192403, except that the specific rotation showed approximately equal and opposite values: (+)-**1**, fraction 1, $[\alpha]_D^{25}$ +18.9 (*c* 0.91, MeOH); (−)-**1**, fraction 2, $[\alpha]_D^{25}$ −19.0 (*c* 0.88, MeOH). The overall process starting from ((±)-)-**1** is accomplished in 67−74% yields (Scheme 2).

As noted above, the literature preparation of (±)-**1**[1] proceeds through a Diels−Alder reaction that generates an approximately 2:1 mixture of *rac*-3-*exo*-isopropyl-2-*endo*-nitrobicyclo[2.2.1]hept-5-ene, (±)-**12**, and *rac*-3-*endo*-isopropyl-2-*exo*-nitrobicyclo[2.2.1]hept-5-ene, (±)-**13** (Scheme 1). Pure (±)-**1** is prepared by careful chromatography on silica gel to remove the undesired *exo* isomer, (±)-**15**. We explored whether the desired (+)-**1** and (−)-**1** could be obtained from the crude mixture of (±)-**1** and (±)-**15**, resulting from the reduction of the mixture of products obtained in the Diels−Alder reaction. Compounds (±)-**2** and (±)-**14** were formed by reaction with this crude material with 4-nitrobenzyl chloroformate (Scheme 3) and profiled the mixture across the same suite of analytical SFC stationary phases and mobile phases examined for the resolution of (±)-**1**. Although we could not identify a system in which the desired *endo* isomers of (±)-**2** were sufficiently separated from the minor byproducts, we did note that the minor *exo* isomers were well-separated from all peaks using a ChiralPak AS-H column (mobile phase: $CO_2$ = 0−20% *i*PrOH). Under these conditions, the enantiomers of (±)-**14** were eluted after the enantiomers of the major isomer, (±)-**2**, which came off as a single peak.



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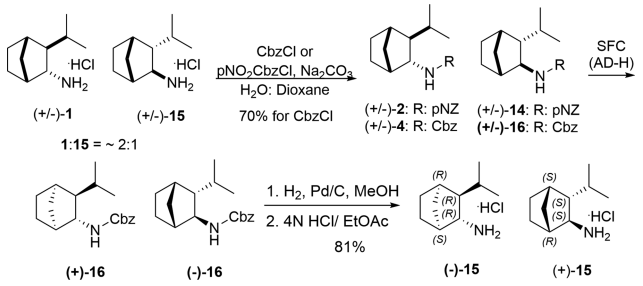
**Scheme 3. Three-Step Preparation of (−)-15 and (+)-15**




Given that the removal of the pNZ generates the *p*-toluidine, we tested whether a similar separation could be achieved using the more convenient Cbz-protecting group for the separation of (±)-**15** and observed a separation profile that could support semi-preparative scale separations ((±)-**4**, (±)-**16**). The separation of the enantiomers of (±)-**16** was executed on the scale, and the individual enantiomers were obtained with good recovery and high enantiopurity ((+)-**16**, fraction 1, $[\alpha]_D^{20}$ +2.0 (*c* 1.03, MeOH), >99% ee; (−)-**16**, fraction 2, $[\alpha]_D^{20}$ −2.8 (*c* 1.01, MeOH), 97.2% ee). Deprotection by catalytic hydrogenation followed by HCl salt formation generated the desired (−)-**15** (fraction 1, $[\alpha]_D^{20}$ −3.0 (*c* 0.10, MeOH)) and (+)-**15** (fraction 2, $[\alpha]_D^{20}$ +5.0 (*c* 0.10, MeOH)) in a high yield. Based on $^1$H NMR chemical shift anisotropy, the conformation of the phenyl ring in **2** and **4** is inferred to lie beneath the *C*3-*endo* proton, whereas this chemical shift effect is not as dramatic in the $^1$H NMR spectra **14** and **16**. Our hypothesis is that this conformation and conformational flexibility account for the observation that CBz protection is effective for separation in this case.

Three methods for the determination of the AC of the isolated enantiomers were pursued. Each method presents different benefits and limitations related to throughput, the requirement for compound derivatization, and the need for specialized equipment. First, we formed a series of Mosher's amides with *α*-methoxy-*α*-(trifluoromethyl)phenylacetic acid (MTPA) and analyzed the change in chemical shift according to Mosher's model, **17**−**20** and **21**−**24** (Table 1).[7−9] This method was previously shown to be effective for the determination of the AC of enantiopure bicyclo[2.2.1]-heptan-2-*endo*-amines.[10] In that work, both the *endo* and *exo* C3 protons exhibited large positive $\delta_{R\text{-}MTPA}-\delta_{S\text{-}MTPA}$ values, implying the 1*S*,2*R*,4*R* configuration, which was confirmed by comparison with an X-ray crystal structure of a cyanoguanidine prepared from the same enantiopure (+)-bicyclo[2.2.1]heptan-2-*endo*-amine.

The (*R*)- and (*S*)-MTPA amides were synthesized with both (+)-**1** and (−)-**1** and the corresponding Mosher's acids.[11,12] The C3 proton of **1** shifted from 1.18 ppm to either 0.58 or 0.52 ppm (ddd, *J* = 9.9, 5.2, 2.0 Hz) depending on the stereochemistry of the Mosher's acid and the amine. These resonances were well-separated and resolved and thus enabled structural assignment from the 1D proton NMR spectra. Compound (+)-**1** is assigned as (1*S*,2*S*,3*S*,4*R*) based on the negative $\delta_{R\text{-}MTPA}-\delta_{S\text{-}MTPA}$ (**18**−**17**) values (Table 1). Compound (−)-**1** showed the opposite relationship of chemical shifts with the diastereomer formed from the (*R*)-MTPA, **19**, displaying a chemical shift of 0.58 ppm, which is more downfield than observed for the S-Mosher's amide, **20** (0.52 ppm), and is therefore assigned as the (1*R*,2*R*,3*R*,4*S*) configuration. Similarly, Mosher's amides (**21**−**24**) were synthesized from (−)-**15** and (+)-**15**, and chemical shift analysis of the C3 proton assigned the AC of (−)-**15** as (1*S*,2*R*,3*R*,4*R*) and (+)-**15** as (1*R*,2*S*,3*S*,4*S*).

Next, we determined the AC of **1** and **15** using vibrational circular dichroism (VCD), a methodology that can be deployed directly on the compounds of interest in the solution phase[13−17] and is particularly effective on compounds with relatively rigid structures.[18,19] High neighborhood similarity (Sfg) values[20] indicated excellent congruence between the calculated and measured spectra for both the free base and HCl salt of **1** and **15** HCl (Figure 1 and Figure S3). The Sfg values were slightly lower when the HCl salt was analyzed due to the higher degree of solvent and/or intermolecular interactions for the charged molecule, which was not modeled in the calculations. The rigidity of the structure overall kept the number of low-energy conformers small, facilitating the calculation of the salt, which featured the Cl ion associated with different hydrogens on the charged nitrogen atom. The

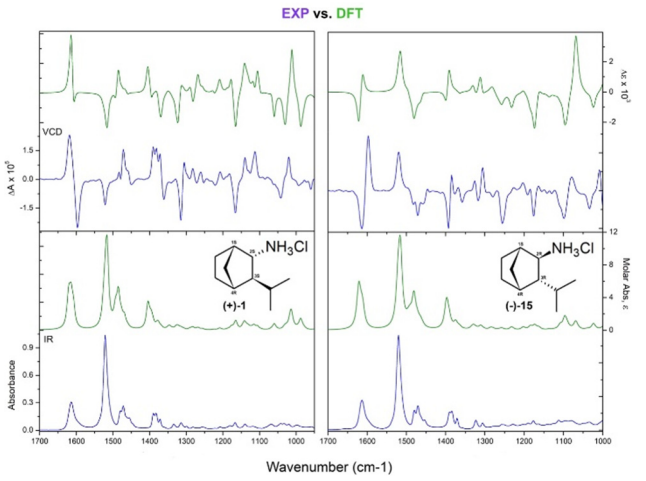



**Figure 1.** Calculated (DFT) and experimental (EXP) VCD and IR spectra for (+)-**1** and (−)-**15**.

**Table 1. Summary of C3-H Chemical Shifts and AC Assignments**[a]

| compound | *δ* C3-*H* | $\delta_{R\text{-}MTPA}-\delta_{S\text{-}MTPA}$ | assignment | compound | *δ* C3-*H* | $\delta_{R\text{-}MTPA}-\delta_{S\text{-}MTPA}$ | assignment |
|---|---|---|---|---|---|---|---|
| (+)-**1** | 1.18 | | (1*S*,2*S*,3*S*,4*R*) | (−)-**15** | 1.53 | | (1*S*,2*R*,3*R*,4*R*) |
| **17** | 0.52 | −0.06 | (+)-**1**; (*R*)-MBTA | **21** | 1.01 | +0.07 | (−)-**15**; (*R*)-MBTA |
| **18** | 0.58 | −0.06 | (+)-**1**; (*S*)-MBTA | **22** | 0.94 | +0.07 | (−)-**15**; (*S*)-MBTA |
| (−)-**1** | 1.18 | | (1*R*,2*R*,3*R*,4*S*) | (+)-**15** | 1.53 | | (1*R*,2*S*,3*S*,4*S*) |
| **19** | 0.58 | +0.06 | (−)-**1**; (*R*)-MBTA | **23** | 0.95 | −0.06 | (+)-15; (*R*)-MBTA |
| **20** | 0.52 | +0.06 | (−)-**1**; (*S*)-MBTA | **24** | 1.01 | −0.06 | (+)-15; (*S*)-MBTA |

[a]Spectra in $CDCl_3$, referenced to $CHCl_3$, acquired at 400 MHz.



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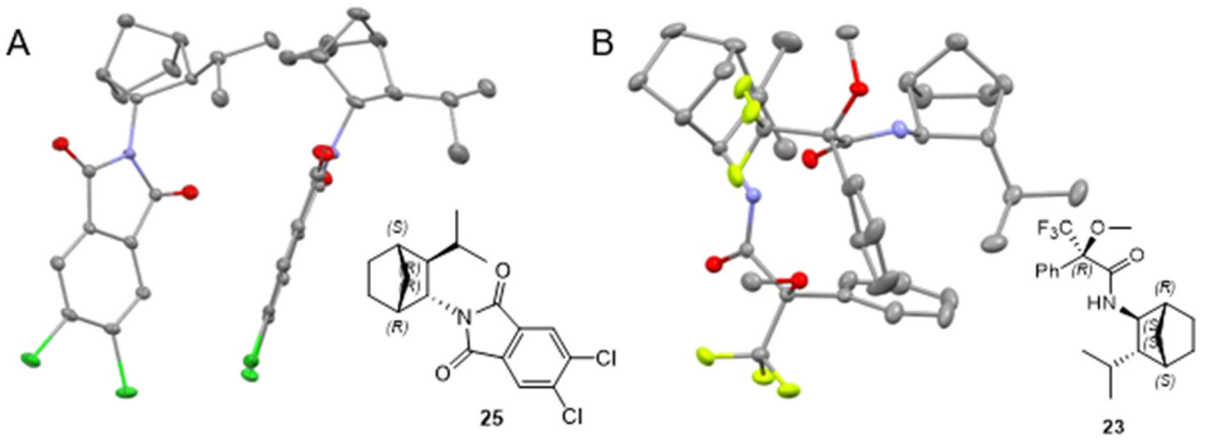


**Figure 2.** Thermal ellipsoid representation of the single-crystal X-ray structures of compounds **25** (A) and **23** (B), drawn at the 50% occupancy level. Hydrogen atoms were omitted for clarity.

experimental spectra of these two states of the molecule differed significantly, necessitating separate calculations for both salt and free base. AC determination by VCD spectroscopy was rapid and reliable and did not require compound derivation.

Finally, we obtained X-ray crystal structures of derivatized (−)-**1** and (+)-**15**. Direct X-ray analysis of the Mosher's amides **17**−**20** could not be performed because the compounds are oils at room temperature and conditions to induce the formation of a solid were not discovered. We, therefore, formed the dichloroisoindoline-1,3-dione, **25** (Figure 2A), which was recrystallized from methanol. In the case of the *exo* isomers, **21**−**24**, the Mosher's amides were solids and X-ray analysis of a crystal of **23** was possible using a crystal obtained by recrystallization from ethanol (Figure 2B). The molecules of **23** contained within the unit cell displayed conformations typical of Mosher's amide structures contained within the Cambridge Structure Database.[9,21] Notable features include the *Z*-amide orientation with the carbonyl synperiplanar to a staggered trifluoromethyl group, the C2-methine proton antiperiplanar to the amide NH, and an inclined phenyl ring with the face directed at the C3-*exo* proton. Details of the SCXRD refinement, data quality, and a summary of the residual values are presented in the Supporting Information.

In conclusion, we have developed a method for the resolution of the enantiomers of **1** that involves the incorporation of the pNZ amine-protecting group. The separation achieved using this method is sufficient to allow for facile resolution of more than 100 g of racemate using standard SFC equipment. The absolute configuration of the enantiomers of **1** was determined by Mosher's amide analysis, VCD spectroscopy, and single-crystal X-ray. Additionally, an approach to the separation of the *exo*-enantiomers, resulting from the Diels−Alder reaction, was developed, and the ACs were determined. We highlight VCD spectroscopy (coupled with ab initio calculations) as a rapid and reliable method for AC determination in [2.2.1]-bicycloheptanamines that can be deployed directly on the HCl salts. These results provide methods for the preparation of all isomeric Diels−Alder products generated from the Diels−Alder reaction of dienophile **3** and cyclopentadiene and provide orthogonal approaches for the determination of AC in these and similar systems.

## EXPERIMENTAL SECTION

All reagents and solvents were purchased from commercial vendors. High-resolution mass spectra were obtained using an Agilent 6545 Q-TOF, Thermo Fisher Scientific LTQ FT Ultra, or Thermo Scientific Q Exactive HF Orbitrap-FTMS instrument. Electron impact (EI) mass spectrometry (MS) was performed on a Waters Acquity spectrometer. $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker 400 MHz and processed with the MestReNova program. Proton and carbon chemical shifts ($\delta$) are reported in ppm relative to internal solvent peak. NMR data are reported as follows: $\delta$, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet); coupling constants in Hz; integration. NMR data were collected at 25 °C. Flash chromatography was performed using 40−60 $\mu$m silica gel (60 Å mesh) on a Teledyne Isco Combiflash Rf system. SFC separations were performed using the Thar SFC350 system Thar SFC100 system, Waters SFC80 semipreparative systems, or Waters UPCC analytical SFC system. The method information is described in the procedures of the respective compounds. Analytical scale SFC condition screening was performed on CHIRALCEL OJ-H, AD-H, AS-H, IC, and OD-H columns (250 mm × 4.6 mm × 5 $\mu$m); flow rate = 1.5 mL/min; mobile phases = MeOH, MeOH + 1% TFA, MeOH + 0.05% $Et_3N$ and iPrOH (3−50%); back pressure =136 bar; column oven temp = 45 °C.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1983233−1983234. Copies of the data can be obtained free of charge from https://www.ccdc.cam.ac.uk/.

**VCD Measurements.** Twenty mg of the free base of (+)-**1** or (−)-**1** was dissolved in 100 $\mu$L of $CDCl_3$ and placed in a $BaF_2$ IR cell with a path length of 100 $\mu$m. Instrumentation was a BioTools ChiralIR 2X w/DualPEM FT-VCD, resolution 4 cm$^{-1}$, PEM focus frequency 1400 cm$^{-1}$. Each enantiomer was measured for 3 h; then the IR spectra were solvent subtracted, and the VCD spectra were corrected with the half-difference method. The HCl salts (+)-**1**, (+)-**1**, (−)-**15**, and (+)-**15** were measured and the data processed in an analogous fashion, at a concentration of 8 mg/100 $\mu$L $CDCl_3$.

**VCD Calculations.** Compound **1** (free base) was searched using GMMX to find the low-energy conformers. Each of the 9 conformers was minimized using Gaussian 09 at the 6311Gdp/B3LYP level with the CPCM solvent (chloroform) model. IR and VCD frequencies were calculated at the same level, then Boltzmann averaged, and plotted with a line width of 6 cm$^{-1}$. IR and VCD spectra were then frequency scaled by a factor of 0.976 and compared to experimental data. Compound **1** (HCl salt) was calculated using the same parameters, again with 9 relevant conformers. Compound **15** was likewise found to have 9 low-energy conformers; *x*-axis scaling factors for the HCl salts were 0.983 and 0.981, respectively. A neighborhood similarity (Sfg) of 95.4 was found for IR and 74.6 for VCD, and an


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enantiomeric similarity index (ESI) of 63.1 was also found.[20] Sfg values for **1** (HCl salt) were 93.3 for the IR and 55.6 for the VCD with an ESI of 42.0. High confidence results were also obtained for **15** (HCl salt) (Sfg 90.0 IR and 66.0 VCD, ESI 53.9) with a strong visual agreement between the calculated and measured spectra.

**X-ray Diffraction.** Low-temperature diffraction data were collected on a Bruker-AXS X8 Kappa Duo diffractometer coupled to a Photon 2 CPAD detector for the structure of compound **25** and a Smart APEX2 CCD detector for the structure of **23**. The data collections were executed with Mo K$\alpha$ radiation ($\lambda$ = 0.71073 Å) from an I$\mu$S microsource, performing $\varphi$-and $\omega$-scans. Both structures were solved by dual-space methods using SHELXT[22] and refined against $F^2$ on all data by full-matrix least-squares with SHELXL-2017,[23] following established refinement strategies.[24] All non-hydrogen atoms were refined anisotropically. Except for the nitrogen-bound H-atoms in the structure of **23**, all hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. Coordinates for the amide-hydrogen atoms in the structure of **23** were taken from the difference Fourier synthesis, and the hydrogen positions in question were subsequently refined semifreely with the help of distance restraints (target N−H distances 0.88(2) Å), while constraining their $U_{iso}$ to 1.2 times the value of the $U_{eq}$ of the nitrogen atoms to which they bind. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups).

*rac-4-Nitrobenzyl-(3-exo-isopropylbicyclo [2.2.1]heptan-2-endo-yl)carbamate, (±)-**2**.* To a solution of *rac*-3-*exo*-isopropybicyclo-[2.2.1]heptan-2-*endo*-amine hydrochloride, (±)-**1**, (70.0 g, 0.36 mol, 1.0 equiv) in dichloromethane (DCM) and water (1:1, 700 mL) was added sodium carbonate ($Na_2CO_3$) (190.8 g, 1.8 mol, 5 equiv) portionwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Then it was cooled to 0 °C, and 4-nitrobenzyl chloroformate (116.4 g, 0.54 mmol, 1.5 equiv) was added portionwise under a positive pressure of $N_2$ gas. The mixture was stirred at room temperature for 16 h. TLC (petroleum ether/ethyl acetate (EtOAc) 20%, $R_f$ = 0.60) indicated that the reaction was completed. The reaction mixture was then diluted with 200 mL of water and extracted with EtOAc (350 mL × 3). The organic phases were collected, washed with brine (350 mL × 2), dried over anhydrous sodium sulphate ($Na_2SO_4$), and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (petroleum ether/EtOAc 1−10% ) to give the compound **2** (120.0 g, 0.30 mol, 98.0% yield) as a white solid. Proton NMR exhibited small "shoulders" upfield of main resonances as was common with all carbamate functionalized compounds in this series. $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 8.21 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 5.20, 5.16 (ABq, *J* = 14.0 Hz, 2H), 4.82 (d, *J* = 7.8 Hz, 1H), 3.67−3.53 (m, 1H), 2.42 (m, 1H), 2.14 (d, *J* = 3.2 Hz, 1H), 1.64−1.57 (m, 1H), 1.50−1.35 (4H), 1.20 (dd, *J* = 10.3, 1.8 Hz, 1H), 1.17−1.09 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.54−0.46 (m, 1H) ppm. $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 154.2, 146.5, 143.2, 127.0, 122.7, 64.0, 57.4, 57.3, 39.8, 38.3, 34.4, 31.1, 29.7, 20.7, 20.0, 19.0. HRMS (ESI/Q-TOF): *m*/*z* calcd for $C_{18}H_{25}N_2O_4$ $[M + H]^+$, 333.1814; found, 333.1814.

*4-Nitrobenzyl ((1S,2S,3S,4R)-3-Isopropylbicyclo[2.2.1]heptan-2-yl)carbamate, (+)-**2** (Fraction 1), and 4-Nitrobenzyl ((1R,2R,3R,4S)-3-Isopropylbicyclo[2.2.1]heptan-2-yl)carbamate, (−)-**2** (Fraction 2).* A total of 120.0 g (0.30 mol) of (±)-**2** was separated using a Thar SFC100 preparative SFC system fitted with a Daicel Chiralpak AD column (250 mm × 25 mm, 10 $\mu$m). The mobile phase was $CO_2$ (A) and isopropanol with 0.1% $NH_3H_2O$ (B) 30% isocratic (flow rate = 70 g/min, back pressure = 100 bar, column temperature = 25 °C), detection at 254 nm. Approximately 360 mg of the sample was injected per purification with a cycle time of 8 min between injections. After separation, the fractions were concentrated via a rotary evaporator at a bath temperature of 40 °C to give compound (+)-**2**, fraction 1 (58.0 g, 0.181 mol, 97% recovery, 99.7% ee by analytical SFC) $[\alpha]_D^{25}$ +21.8 (*c* 0.72, $CH_3CN$), as a white solid and (−)-**2**, fraction 2 (57.0 g, 0.17 mol, 95.0% recovery, 99.8% ee by analytical SFC) $[\alpha]_D^{25}$ −20.5 (*c* 1.16, $CH_3CN$), as a white solid.

*(1S,2S,3S,4R)-3-Isopropylbicyclo[2.2.1]heptan-2-amine hydrochloride, (+)-**1** (Fraction 1), and (1R,2R,3R,4S)-3-Isopropylbicyclo-[2.2.1]heptan-2-amine hydrochloride, (−)-**1** (Fraction 2).* To a stirred solution of (+)-**2** (58.0 g, 0.17 mol, 1.0 equiv) in tetrahydrofuran (THF) (1.2 L) was added Pd/C (6.0 g, 10 wt %) under Ar. The mixture was solidified in liquid nitrogen and the headspace of the flask exchanged with $H_2$ gas. The reaction was stirred at 25 °C for 16 h under $H_2$ (1 atm). TLC (petroleum ether/EtOAc 10%, $R_f$ = 0) showed that the reaction was completed. The reaction mixture was filtered through Celite, and the filtrate was carefully concentrated to afford a crude that was purified by column chromatography (column size = 31.2 cm (height) × 9.9 cm diameter, 700 g of silica gel 200−300 mesh). The column was eluted with 1 L of DCM at which point *p*-toluidine was detectable on TLC (PMA stain). The desired product was eluted by increasing the percentage of methanol (MeOH) in the mobile phase to 2% over the course of the next 6 L of DCM eluted through the column. Prior to concentration, HCl (4 N in 1,4-dioxane, 190 mL) was added, and the solvent was evaporated to yield 25.0 g (0.13 mol, 76.5%) of (+)-**1** as a white solid. Analytical characterization was identical to an authentic standard of **1** other than the optical rotation ((+)-**1** = $[\alpha]_D^{25}$ +18.9 (*c* 0.91, MeOH); (−)-**1** = $[\alpha]_D^{25}$ −19.0 (*c* 0.88, MeOH). $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 8.51 (s, 3H), 3.20 (ddq (broad), *J* = 4.8, ∼3, ∼5 Hz, 1H), 2.63 (dd, *J* = 4.8, ∼4.5 Hz, 1H), 2.20 (d, *J* = 3.6 Hz,1H), 1.94−1.88 (m, 1H), 1.45−1.62 (m, 5H), 1.27 (d, *J* = 10.0 Hz, 1H), 1.17 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 57.5, 55.4, 40.4, 39.5, 36.0, 31.4, 29.7, 21.6, 21.2, 20.7. HRMS (ESI/Q-TOF): *m*/*z* calcd for $C_{10}H_{20}N$ $[M + H]^+$, 154.1596; found, 154.1587 ((+)-**1**) and 154.1584 ((−)-**1**).

*rac-Benzyl-(3-exo-isopropylbicyclo[2.2.1]heptan-2-endoyl)-carbamate, (±)-**4**.* To a stirred solution of *rac*-3-*exo*-isopropybicyclo-[2.2.1]heptan-2-*endo*-amine hydrochloride, (±)-**1**, (37 mg, 0.196 mmol, 1.00 equiv) in water (1 mL) was added $Na_2CO_3$ (22 mg, 0.206 mmol, 1.05 equiv). The reaction mixture was cooled down to 0 °C, and benzyl chloroformate (0.028 mL, 0.196 mmol, 1.00 equiv) was slowly added. After 20 min of stirring, additional water (0.5 mL) was added, and the reaction mixture was stirred for another hour. After the reaction was completed, diethyl ether was added, and the product was extracted 3 times with diethyl ether. The combined organic layers were washed with HCl (1 M) and NaOH (1 M), dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, and concentrated. The crude residue was purified with flash column chromatography on silica gel (hexane/EtOAc) to afford the desired compound (±)-**4** (25 mg, 44% yield) as a white solid. $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.36 (m, 5H), 5.11 (m, 2H), 4.79 (d, *J* = 7.9 Hz, 1H), 3.62 (m, 1H), 2.43 (m, 1H), 2.12 (d, *J* = 4.2 Hz, 1H), 1.65−1.57 (m, 2H), 1.51 (m, 4H), 1.22 (dd, *J* = 10.1 Hz, 2.1 Hz, 1H), 1.14 (m, 1H), 0.89 (m, 6H), 0.49 (m, 1H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 155.9, 136.8, 128.7, 128.2, 66.7, 58.5, 58.4, 41.0, 39.4, 35.6, 32.2, 30.9, 21.9, 21.2, 20.2. HRMS (ESI/Q-TOF): *m*/*z* calcd for $C_{18}H_{26}NO_2$ $[M + H]^+$, 288.1963; found, 288.1953.

*rac-4-Bromobenzyl-(3-exo-isopropylbicyclo[2.2.1]heptan-2-endoyl)carbamate, (±)-**5**.* To a stirred solution of *rac*-3-*exo*-isopropybicyclo[2.2.1]heptan-2-*endo*-amine hydrochloride, (±)-**1** (30 mg, 0.158 mmol, 1.00 equiv), and $Na_2CO_3$ (34 mg, 0.316 mmol, 2.00 equiv) in 1,4-dioxane (1 mL) was added (4-bromophenyl)methyl chloroformate (24 $\mu$L, 0.158 mmol, 1.00 equiv). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was concentrated. The crude residue was purified with flash column chromatography (hexane/EtOAc 0−25%) to afford the desired (±)-**5** (9 mg, 16%) as a white solid. $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.51 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.03 (m, 2H), 4.76 (d, *J* = 7.9 Hz, 1H), 3.58 (m, 1H), 2.42 (s, 1H), 2.13 (d, *J* = 3.6 Hz, 1H), 1.64−1.58 (m, 3H), 1.49−1.32 (m, 4H), 1.19 (dd, *J* = 10.3, 2.0 Hz, 1H), 1.16−1.07 (m, 1H), 0.88 (m, 6H), 0.51−0.43 (m, 1H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 155.7, 145.4, 131.8, 129.8, 65.8, 58.54, 58.45, 41.0, 39.4, 35.6, 35.4, 32.2, 30.8, 21.9, 21.2,


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20.2. HRMS (ESI/Q-TOF): $m/z$ calcd for $C_{18}H_{25}BrNO_2$ $[M + H]^+$, 366.1069; found, 366.1063.

*rac-(9H-Fluoren-9-yl)methyl-(3-exo-isopropylbicyclo[2.2.1]-heptan-2-endoyl)carbamate, (±)-**6**.* To a stirred solution of *rac*-3-*exo*-isopropybicyclo[2.2.1]heptan-2-*endo*-amine hydrochloride, (±)-**1** (37 mg, 0.196 mmol, 1.00 equiv), in 1,4-dioxane (1 mL) was added $Na_2CO_3$ (1.0 M in water, 0.21 mL, 0.206 mmol, 1.05 equiv). At 0 °C, a solution of 9*H*-fluoren-9-ylmethyl chloroformate (51 mg, 0.196 mmol, 1.00 equiv) in 1,4-dioxane (0.2 mL) was added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. Water was poured into the reaction mixture, and the product was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was purified with flash column chromatography (hexane/ EtOAc 0−30%) to afford the desired (±)-**6** as a white solid (30 mg, 41% yield). $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.77 (d, $J$ = 7.5 Hz, 2H), 7.64−7.56 (m, 2H), 7.45−7.36 (m, 2H), 7.32 (ddd, $J$ = 7.4, 7.4, 1.2 Hz, 2H), 4.79 (d, $J$ = 7.5 Hz, 1H), 4.44 (m, 2H), 4.23 (m, 1H), 3.59 (m, 1H), 2.42 (s, 1H), 2.13 (m, 1H), 1.68−1.50 (m, 1H), 1.48−1.30 (m, 3H), 1.22 (s, 2H), 0.95−0.83 (m, 6H), 0.50 (ddd, $J$ = 9.8, 5.4, 2.0 Hz, 1H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$): $\delta$ 155.6, 143.93, 143.98, 140.7, 127.6, 127.0, 125.25, 125.21, 120.1, 65.0, 58.1, 54.3, 46.8, 40.6, 39.5, 38.8, 36.2, 35.0, 31.7, 29.9, 21.7, 20.8, 19.7. HRMS (ESI/DART-FTMS): $m/z$ calcd for $C_{25}H_{30}NO_2$ $[M + Na]^+$, 376.2277; found, 376.2270.

*rac-(3-exo-Isopropylbicyclo[2.2.1]heptan-2-endoyl)-4-methyl-benzenesulfonamide, (±)-**7**.* To a stirred solution of *rac*-3-*exo*-isopropybicyclo[2.2.1]heptan-2-*endo*-amine hydrochloride, (±)-**1** (39 mg, 0.254 mmol, 1.00 equiv), in dry DCM (1 mL) at 0 °C and under $N_2$ were added triethylamine (0.071 mL, 0.509 mmol, 2.00 equiv) and a solution of 4-methylbenzenesulfonyl chloride (53 mg, 0.280 mmol, 1.10 equiv) in DCM (0.2 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 2.5 days. Water was poured into the reaction mixture, and the product was extracted with DCM. The organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was purified with flash column chromatography (hexane/EtOAc 0−15%) to afford the desired (±)-**7** as a white solid (36 mg, 57% yield). $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.77 (d, $J$ = 8.2 Hz, 2H), 7.28 (d, $J$ = 8.2 Hz, 2H), 4.74 (d, $J$ = 6.7 Hz, 1H), 3.13 (ddd, $J$ = 6.8, 5.3, 3.9 Hz, 1H), 2.42 (s, 3H), 2.11−2.01 (m, 2H), 1.56−1.42 (m, 2H), 1.34−1.17 (m, 3H), 1.10 (m, 2H), 0.82 (d, $J$ = 6.5 Hz, 3H), 0.69 (d, $J$ = 6.6 Hz, 3H), 0.51 (ddd, $J$ = 9.5, 5.1, 2.1 Hz, 1H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 143.4, 137.9, 129.7, 127.4, 60.4, 58.7, 40.8, 38.9, 35.4, 32.2, 30.6, 21.80, 21.69, 20.9, 20.0. HRMS (ESI/Q-TOF): $m/z$ calcd for $C_{17}H_{26}NO_2S$ $[M + H]^+$, 308.1684; found, 308.1680.

*rac-(3-exo-Isopropylbicyclo[2.2.1]heptan-2-endoyl)-2-nitroben-zenesulfonamide, (±)-**8**.* To a stirred solution of *rac*-3-*exo*-isopropybicyclo[2.2.1]heptan-2-*endo*-amine hydrochloride, (±)-**1** (30 mg, 0.196 mmol, 1.00 equiv) in dry DCM (1 mL), at 0 °C and under $N_2$ was added triethylamine (0.055 mL, 0.391 mmol, 2.00 equiv) and a solution of 2-nitrobenzenesulfonyl chloride (48 mg, 0.215 mmol, 1.10 equiv) in DCM (0.2 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. Water was poured into the reaction mixture, and the product was extracted with DCM. The organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to afford the desired (±)-**8** as a white solid (37 mg, 56% yield). $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 8.19−8.12 (m, 1H), 7.88−7.81 (m, 1H), 7.79−7.68 (m, 2H), 5.41 (d, $J$ = 7.0 Hz, 1H), 3.37 (ddd, $J$ = 7.0, 5.4, 4.0 Hz, 1H), 2.25−2.04 (m, 2H), 1.63−1.42 (m, 2H), 1.42−1.07 (m, 6H), 0.85 (d, $J$ = 6.6 Hz, 3H), 0.70 (d, $J$ = 6.6 Hz, 3H), 0.63 (ddd, $J$ = 9.7, 5.2, 2.1 Hz, 1H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 147.8, 134.9, 133.4, 132.8, 130.8, 125.4, 61.4, 58.2, 41.1, 38.8, 35.4, 32.0, 30.4. 21.7, 20.7, 19.6. HRMS (ESI/Q-TOF): $m/z$ calcd for $C_{16}H_{23}N_2O_4S$ $[M + H]^+$, 339.1378; found, 339.1379.

*rac-N,N-Dibenzyl-3-exo-isopropylbicyclo[2.2.1]heptan-2-endo-amine, (±)-**9**.* To a stirred solution of *rac*-3-*exo*-isopropybicyclo-[2.2.1]heptan-2-*endo*-amine hydrochloride, (±)-**1** (0.3 g, 1.960 mmol, 1.0 equiv), in *N*,*N*-dimethylformamide (DMF) (3 mL) was added potassium carbonate ($K_2CO_3$) (0.541 g, 3.92 mmol, 2 equiv), and the reaction mixture was stirred for 15 min at room temperature. To this, benzyl bromide (0.268 g, 1.568 mmol, 0.8 equiv) was added dropwise, and the solution was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was diluted with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated to get crude material, which was purified using column chromatography (hexanes/ EtOAc 10%) to obtain (0.100 g, 0.299 mmol, 15%) (±)-**9** as a white solid. $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.37−7.29 (m, 8H), 7.27−7.22 (m, 2H), 3.76−3.67 (abq, 4H), 2.76 (m, 1H), 2.56 (m, 1H), 2.15−2.08 (m, 2H), 1.65−1.57 (m, 1H), 1.52−1.42 (m, 2H), 1.39−1.23 (m, 3H), 1.18−1.09 (m, 2H), 0.87 (d, $J$ = 6.7 Hz, 3H), 0.79 (d, $J$ = 6.8 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 140.2, 129.0, 128.0, 126.5, 68.3, 55.7, 52.3, 40.4, 38.4, 36.0, 32.1, 31.0, 22.3, 22.2, 20.0). HRMS (ESI/Q-TOF): $m/z$ calcd for $C_{24}H_{30}N_4$ $[M + H]^+$, 334.2535; found, 334.2567.

*rac-(3-exo-Isopropylbicyclo[2.2.1]heptan-2-endoyl)isoindoline-1,3-dione, (±)-**10**.* To a pressure vessel *rac*-3-*exo*-isopropybicyclo-[2.2.1]heptan-2-*endo*-amine hydrochloride, (±)-**1** (0.150 g, 0.980 mmol, 1 equiv), in (DMF) (2 mL) was added isobenzofuran-1,3-dione (0.156 g, 1.043 mmol, 1.6 equiv), and the reaction mixture was stirred and heated at 180 °C with an aluminum heating block for 3 h. After completion of the reaction, reaction mixture was diluted with water and extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated to get crude, which was purified by column chromatography (hexanes/ EtOAc 3%). The desired product (±)-**10** (160 mg, 0.564 mmol, 58%) was obtained as a white solid. $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.84 (dd, $J$ = 5.4, 3.0 Hz, 2H), 7.74 (dd, $J$ = 5.4, 3.0 Hz, 2H), 4.12 (ddd, $J$ = 6.0, 4.0, 2.1 Hz, 1H), 2.52−2.48 (m, 1H), 2.48−2.44 (m, 1H), 2.36 (d, $J$ = 4.4 Hz, 1H), 1.80−1.63 (m, 2H), 1.62−1.53 (m, 2H), 1.24 (dd, $J$ = 10.1, 1.8 Hz, 1H), 0.96 (d, $J$ = 6.5 Hz, 3H), 0.75 (d, $J$ = 6.6 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 169.6, 133.8, 131.9, 123.0, 60.7, 46.7, 43.2, 40.0, 35.1, 32.9, 29.7, 23.3, 21.7, 19.7. HRMS (ESI/Q-TOF): $m/z$ calcd for $C_{18}H_{22}NO_2$ $[M + H]^+$, 284.1650; found, 284.1631.

*rac-(3-exo-Isopropylbicyclo[2.2.1]hept-5-en-2-endoyl)-acetamide, (±)-**11**.* To a stirred solution of crude *rac*-3-isopropyl-2-nitrobicyclo[2.2.1]hept-5-ene (*endo*/*exo* $NO_2$ is ∼2:1) (5.39 g, 27.6 mmol, 1.00 equiv) in a (1:1) mixture of MeOH (50 mL) and aqueous solution of saturated ammonium formate (50 mL) was added zinc dust (9.02 g, 138 mmol, 5.00 equiv) portionwise over a period of 10 min at room temperature. The resulting reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a Celite pad and washed with MeOH (2 × 30 mL). The organic layer was basified with saturated ammonium bicarbonate (150−160 mL) until pH = 9−10. The resultant aqueous layer was extracted with DCM (2 × 90 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered through Celite, and evaporated under a vacuum at a low temperature to get crude product *rac*-3-isopropylbicyclo[2.2.1]hept-5-en-2-amine (4 g, 26.45 mmol, 96%). It was used in the next step without further purification. MS (ESI/SQ) $m/z$: calcd for $C_{12}H_{18}N[M+H]^+$, 152.1; found, 152.2.

To a stirred solution of the crude *rac*-3-isopropylbicyclo[2.2.1]-hept-5-en-2-amine (2.00 g, 13.2 mmol, 1.00 equiv) and triethyl amine (4.6 mL, 33.1 mmol, 2.50 equiv) in toluene (30 mL) was added acetyl chloride (1.4 mL, 19.8 mmol, 1.50 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, it was diluted by the addition of water (30 mL), and the layers were separated. The aqueous layer was extracted with DCM (2 × 50 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered through Celite, and evaporated to provide crude material, which was purified by column chromatography (hexanes/ EtOAc 25%) to provide *rac*-(3-*exo*-isopropylbicyclo[2.2.1]-hept-5-en-2-endoyl)acetamide, **11** (0.65 g, 3.36 mmol, 25%) as a white solid which eluted before the *rac*-(3-*endo*-isopropylbicyclo-[2.2.1]hept-5-en-2-exoyl)acetamide isomer. $^1$H NMR (400 MHz,


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chloroform-*d*): δ 6.42 (dd, *J* = 5.8, 3.2 Hz, 1H), 6.06 (dd, *J* = 5.7, 2.8 Hz, 1H), 5.15 (bs, 1H), 4.16 (m, 1H), 3.00 (m, 1H), 2.73 (m, 1H), 1.93 (s, 3H), 1.58−1.49 (m, 2H), 1.44 (m, 1H), 0.97 (m, 6H), 0.58 (ddd, *J* = 10.3, 4.0, 2.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 169.0, 140.7, 132.9, 57.6, 54.9, 46.4, 45.6, 44.8, 32.4, 23.5, 21.9, 21.8. HRMS (ESI/Q-TOF): *m*/*z* calcd for $C_{12}H_{20}NO$ $[M + H]^+$, 194.1545; found, 194.1532.

*Benzyl ((1S,2R,3R,4R)-3-Isopropylbicyclo[2.2.1]heptan-2-yl)-carbamate, (+)-**16**, and Benzyl ((1R,2S,3S,4S)-3-Isopropylbicyclo-[2.2.1]heptan-2-yl)carbamate, (−)-**16**.* To a mixture of crude **1** and **15** (7.82 g, 41.3 mmol, 1 equiv, ratio ∼2:1 *endo*/*exo*) in DCM (80 mL) and water (80 mL) were added benzyl chloroformate (8.45 g, 49.6 mmol, 1.2 equiv) and then $Na_2CO_3$ (13.1 g, 124 mmol, 3 equiv) dropwise at 0 °C under $N_2$. The mixture was stirred at 25 °C for 12 h. TLC (plate 1, DCM/methanol 20%) showed the material disappeared, and TLC (plate 2, petroleum ether/EtOAc 20%, $R_f$ = 0.43) showed new spots formed. The reaction mixture was diluted with water (40 mL) and extracted with DCM (25 mL) three times. The combined organic layers were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (petroleum ether/EtOAc 20%) to give 8.31 g of (±)-**4** and (±)-**16** as a mixture (28.9 mmol, 70% yield). This mixture was purified using a Thar 350 preparative SFC (SFC-18) system: column = ChiralPak AS, 300 mm × 50 mm I.D., 10 μm, mobile phase = A for $CO_2$ and B for isopropanol, gradient = B 20%, flow rate = 200 mL/min, back pressure = 100 bar, column temperature = 38 °C, wavelength = 220 nm, cycle time = ∼4.5 min. The compound was dissolved in 100 mL of ethanol/DCM; injection = 8 mL per injection. The separation could be completed in less than one hour of instrument time.

After the separation, the fractions were concentrated via rotary evaporator at a bath temperature of 40 °C to give (+)-**16** (1.50 g, 5.21 mmol, 76%) and (−)-**16** (1.60 g, 5.55 mmol, 80%) as white solids (yields estimated based on a maximum theoretical yield of each enantiomer from crude starting material). Analytical characterizations of (+)-**16** and (−)-**16** were identical other than the optical rotation: ((+)-**16** $[\alpha]_D^{20}$ +2.0 (*c* 1.03, MeOH), 98.2% ee by analytical SFC; (−)-**16** $[\alpha]_D^{20}$ −2.8 (*c* 1.01, MeOH), 97% ee by analytical SFC. $^1H$ NMR (400 MHz, chloroform-*d*): δ 7.36−7.28 (m, 5H), 5.11−5.05 (abq, 2H), 4.65 (d, *J* = 7.9 Hz, 1H), 3.08 (m, 1H), 2.20 (m, 2H), 1.57−1.27 (m, 5H), 1.24 (d, *J* = 9.9 Hz, 1H), 1.20−1.14 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.88 (m, 1H), 0.84 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 155.3, 136.7, 128.5, 128.13, 128.09, 66.5, 60.1, 59.0, 43.9, 38.4, 36.8, 29.8, 26.7, 21.9, 21.53, 21.50. HRMS (ESI/DART-FTMS): *m*/*z* calcd for $C_{18}H_{26}NO_2$ $[M + H]^+$, 288.1963; found, 288.1959.

*(1S,2R,3R,4R)-3-Isopropylbicyclo[2.2.1]heptan-2-amine Hydrogen Chloride, (−)-**15**, and (1R,2S,3S,4S)-3-Isopropylbicyclo[2.2.1]-heptan-2-amine Hydrogen Chloride, (+)-**15**.* To a solution of benzyl ((1*S*,2*R*,3*R*,4*R*)-3-isopropylbicyclo[2.2.1]heptan-2-yl)carbamate, (+)-**16** (500 mg, 1.74 mmol, 1 equiv), in MeOH (5 mL) was added Pd/C (200 mg, 1.9 mmol, 0.1 equiv) under a $N_2$ atmosphere. The mixture was then stirred at room temperature for 16 h under $H_2$ gas bubbling. The reaction mixture was filtered through Celite and concentrated under a vacuum to get the crude, which was used directly without further purification. The residue was then dissolved in EtOAc (5 mL), and HCl (4 M in EtOAc, 3 mL) was added dropwise at 0 °C. The resultant mixture was then stirred at room temperature for 10 min and then concentrated *in vacuo* to give the crude product. The crude product was triturated with methyl *tert*-butyl ether (MTBE) at 25 °C for 15 min and then filtered. The solid was washed with MTBE, and the filter cake was dried *in vacuo* to give (−)-**15** (267 mg, 1.41 mmol, 81% yield) as a white solid. Analytical characterization of (−)-**15** and (+)-**15** was identical other than the optical rotation: (−)-**15** = $[\alpha]_D^{20}$ −3.0 (*c* 1.00, MeOH); (+)-**15** = $[\alpha]_D^{20}$ +5.0 (*c* 1.00, MeOH). $^1H$ NMR (400 MHz, chloroform-*d*): δ 8.38 (bs, 3H), 2.75 (m, 1H), 2.56 (d, *J* = 5.0 Hz, 1H), 2.39 (dd, *J* = ∼4.5, ∼4.5, 1H), 2.02 (dt, *J* = 10.7, 1.9 Hz, 1H), 1.72−1.58 (m, 1H), 1.54 (dt, *J* = 10.3, 3.3 Hz, 1H), 1.48−1.25 (m, 4H), 1.18- 1.11 (m, 1H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 77.3, 77.0, 76.7, 59.7, 56.1, 42.0, 39.3, 36.5, 29.4, 26.8, 22.8, 21.4, 21.1. HRMS (ESI/Q-TOF): *m*/*z* calcd for $C_{10}H_{20}N$ $[M + H]^+$, 154.1596; found, 154.1603 ((−)-**15**) and 154.1584 ((+)-**15**).

*(R)-3,3,3-Trifluoro-N-((1S,2S,3S,4R)-3-isopropylbicyclo[2.2.1]-heptan-2-yl)-2-methoxy-2-phenylpropanamide, **17**.* Representative synthesis of the Mosher's acid chloride:[11] to a solution of (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (30 mg, 0.128 mmol, 1.0 equiv) in *n*-hexane (0.6 mL) were added DMF (2 μL, 0.013 mmol, 0.1 equiv) and oxalyl dichloride (0.05 mL, 0.61 mmol, 4.8 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The heterogeneous mixture was filtered to remove the solid, and the filtrate was concentrated to provide the crude Mosher's acid chloride (35 mg), which was used directly without further purification.

Representative synthesis of Mosher's amide: to a stirred solution of (+)-**1** (10 mg, 0.053 mmol, 1.00 equiv) and triethylamine e (22 μL, 0.158 mmol, 3.00 equiv) in DCM (0.50 mL) was added (*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoyl chloride (15 mg, 0.058 mmol, 1.10 equiv). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and purified with flash column chromatography (silica gel, hexanes/EtOAC 0−30%) to afford 10 mg (51% yield) of the desired **17** as a colorless oil. $^1H$ NMR (400 MHz, chloroform-*d*): δ 7.55−7.49 (m, 2H), 7.40−7.35 (m, 3H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.83 (m, 1H), 3.45 (q, *J* = 1.6 Hz, 3H), 2.50 (m, 1H), 2.16 (d, 3.6 Hz, 1H), 1.61 (m, 1H), 1.46 (m, 3H), 1.37 (m, 1H), 1.24−1.19 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.52 (ddd, *J* = 9.9, 5.2, 2.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 165.7, 132.9, 129.5, 128.5, 127.7, 125.3, 122.5 58.2, 56.8, 55.3, 41.1, 39.5, 35.8, 32.1, 30.7, 21.9, 21.3, 20.1. HRMS (ESI/Q-TOF): *m*/*z* calcd for $C_{20}H_{27}F_3NO_2$ $[M + H]^+$, 370.1994; found, 370.1984.

*(S)-3,3,3-Trifluoro-N-((1S,2S,3S,4R)-3-isopropylbicyclo[2.2.1]-heptan-2-yl)-2-methoxy-2-phenylpropanamide, **18**.* Starting amount of (+)-**1**: 10 mg, 0.053 mmol, 1.00 equiv. Isolated yield: colorless oil (9 mg, 0.024 mmol, 46% yield). $^1H$ NMR (400 MHz, chloroform-*d*): δ 7.55−7.49 (m, 2H), 7.43−7.35 (m, 3H), 6.63 (d, *J* = 7.7 Hz, 1H), 3.83 (m, 1H), 3.44 (q, *J* = 1.6 Hz, 3H), 2.50 (m, 1H), 2.16 (d, 3.6 Hz, 1H), 1.59 (m, 2H), 1.51−1.45 (m, 1H), 1.45−1.36 (m, 1H), 1.24−1.11 (m, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.58 (ddd, *J* = 10.0, 5.3, 2.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 165.9, 133.1, 129.5, 128.6, 127.8, 125.3, 122.5, 58.2, 56.9, 55.2, 40.7, 39.5, 35.7, 32.2, 30.8, 21.9, 21.2, 20.1. HRMS (ESI/DART-FTMS): *m*/*z* calcd for $C_{20}H_{27}F_3NO_2$ $[M + H]^+$, 370.1994; found, 370.1984.

*(R)-3,3,3-Trifluoro-N-((1R,2R,3R,4S)-3-isopropylbicyclo[2.2.1]-heptan-2-yl)-2-methoxy-2-phenylpropanamide, **19**.* Starting amount of (−)-**1**: 12 mg, 0.063 mmol, 1.00 equiv. Isolated yield: colorless oil (14 mg, 0.038 mmol, 60% yield). $^1H$ NMR (400 MHz, chloroform-*d*): δ 7.56−7.47 (m, 2H), 7.42−7.33 (m, 3H), 6.63 (d, *J* = 7.9 Hz, 1H), 3.87−3.80 (m, 1H), 3.44 (d, *J* = 1.6 Hz, 3H), 2.49 (m, 1H), 2.16 (d, *J* = 4.2 Hz, 1H), 1.65−1.52 (m, 2H), 1.49 (m, 1H), 1.44−1.29 (m, 1H), 1.23−1.12 (m, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.58 (ddd, *J* = 10.0, 5.3, 1.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 165.9, 133.1, 129.5, 128.6, 127.8, 125.4, 122.5, 58.2, 56.9, 55.2, 40.7, 39.5, 35.7, 32.2, 30.8, 21.9, 21.2, 20.1. HRMS (ESI/DART-FTMS): *m*/*z* calcd for $C_{20}H_{27}F_3NO_2$ $[M + H]^+$, 370.1994; found, 370.1984

*(S)-3,3,3-Trifluoro-N-((1R,2R,3R,4S)-3-isopropylbicyclo[2.2.1]-heptan-2-yl)-2-methoxy-2-phenylpropanamide, **20**.* Starting amount of (−)-**1**: 12 mg, 0.063 mmol, 1.00 equiv. Isolated yield: colorless oil (14 mg, 0.038 mmol, 60% yield). $^1H$ NMR (400 MHz, chloroform-*d*): δ 7.55−7.49 (m, 2H), 7.41−7.35 (m, 3H), 6.64 (d, *J* = 8.2 Hz, 1H), 3.83 (m, 1H), 3.45 (q, *J* = 1.6 Hz, 3H), 2.50 (m, 1H), 2.16 (d, *J* = 3.8 Hz, 1H), 1.61 (m, 2H), 1.52−1.41 (m, 2H), 1.36 (m, 1H), 1.22 (m, 2H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.52 (ddd, *J* = 9.9, 5.2, 2.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*): δ 165.7, 132.9, 129.5, 128.5, 127.7, 125.4, 122.5, 58.2, 56.8, 55.2, 41.1, 39.5, 35.8, 32.1, 30.7, 21.9, 21.3, 20.1. HRMS (ESI/


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DART-FTMS): $m/z$ calcd for $C_{20}H_{27}F_3NO_2$ $[M + H]^+$, 370.1994; found, 370.1988.

*(R)-3,3,3-Trifluoro-N-((1S,2R,3R,4R)-3-isopropylbicyclo[2.2.1]-heptan-2-yl)-2-methoxy-2-phenylpropanamide,* ***21***. Starting amount of (−)-**15**: 10 mg, 0.053 mmol, 1.00 equiv). Isolated yield: white solid (12 mg, 0.033 mmol, 62% yield). $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.52−7.50 (m, 2H), 7.41−7.39 (m, 3H), 6.58 (d, $J$ = 8.0 Hz, 1H), 3.42−3.41 (m, 1H), 3.38 (q, $J$ = 1.6 Hz, 3H), 2.28−2.26 (m, 1H), 2.15 (d, $J$ = 4.0 Hz, 1H), 1.57−1.39 (m, 4H), 1.33−1.18 (m, 3H), 1.08−1.00 (m, 1H), 0.94 (d, $J$ = 4.0 Hz, 3H), 0.88 (d, $J$ = 8.0 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 164.8, 132.9, 129.4, 128.5, 127.7, 123.8, 83.9, 58.9, 58.3, 54.9, 43.5, 38.5, 37.0, 29.7, 26.8, 21.8, 21.5, 21.4. HRMS (ESI/DART-FTMS): $m/z$ calcd for $C_{20}H_{27}F_3NO_2$ $[M + H]^+$, 370.1994; found, 370.1988.

*(S)-3,3,3-Trifluoro-N-((1S,2R,3R,4R)-3-isopropylbicyclo[2.2.1]-heptan-2-yl)-2-methoxy-2-phenylpropanamide,* ***22***. Starting amount of (−)-**15**: 10 mg, 0.053 mmol, 1.00 equiv. Isolated yield: white solid (11 mg, 0.030 mmol, 56% yield). $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.52−7.50 (m, 2H), 7.38−7.36 (m, 3H), 6.51 (d, $J$ = 8.0 Hz, 1H), 3.45−3.43 (m, 1H), 3.36 (q, $J$ = 1.6 Hz, 3H), 2.28−2.26 (m, 1H), 2.20 (d, $J$ = 4.0 Hz, 1H), 1.58−1.54 (m, 1H), 1.48−1.37 (m, 3H), 1.37−1.29 (m, 2H), 1.25−1.20 (m, 2H), 0.98−0.92 (m, 1H), 0.82 (dd, $J$ = 4.0, 8.0 Hz, 6H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 164.7, 132.8, 129.4, 128.4, 127.6, 123.9, 83.9, 58.8, 58.2, 54.9, 43.8, 38.5, 37.0, 29.6, 26.9, 21.9, 21.4. HRMS (ESI/DART-FTMS): $m/z$ calcd for $C_{20}H_{27}F_3NO_2$ $[M + H]^+$, 370.1994; found, 370.1984.

*(R)-3,3,3-Trifluoro-N-((1R,2S,3S,4S)-3-isopropylbicyclo[2.2.1]-heptan-2-yl)-2-methoxy-2-phenylpropanamide,* ***23***. Starting amount of (+)-**15**: 100 mg, 0.636 mmol, 1.00 equiv. Isolated yield: white solid (137 mg, 65% yield). $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.55−7.47 (m, 2H), 7.41−7.35 (m, 3H), 6.54 (d, $J$ = 5.5 Hz, 1H), 3.43 (d, $J$ = 1.6 Hz, 3H), 3.37 (dd, $J$ = 8.4, 4.4 Hz, 1H), 2.26 (s, 1H), 2.21 (d, $J$ = 4.8 Hz, 1H), 1.55 (dq, $J$ = 8.9, 6.0, 4.5 Hz, 1H), 1.49−1.34 (m, 3H), 1.31 (m, 2H), 1.24 (m, 1H), 1.02−0.91 (m, 1H), 0.87−0.78 (m, 6H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$): $\delta$ 164.7, 132.8, 129.4, 128.4, 127.6, 123.9, 83.9, 58.8, 58.2, 54.9, 43.8, 38.5, 37.0, 29.6, 26.9, 21.9, 21.4. HRMS (ESI/DART-FTMS): $m/z$ calcd for $C_{20}H_{27}F_3NO_2$ $[M + H]^+$, 370.1994; found, 370.1986.

*(S)-3,3,3-Trifluoro-N-((1R,2S,3S,4S)-3-isopropylbicyclo[2.2.1]-heptan-2-yl)-2-methoxy-2-phenylpropanamide,* ***24***. Starting amount of (+)-**15**: 10 mg, 0.053 mmol, 1.00 equiv. Isolated yield: white solid (13 mg, 66% yield). $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.56−7.48 (m, 2H), 7.45−7.33 (m, 3H), 6.55 (d, $J$ = 6.6 Hz, 1H), 3.41 (d, $J$ = 1.6 Hz, 3H), 3.39−3.35 (m, 1H), 2.26 (s, 1H), 2.14 (d, $J$ = 4.8 Hz, 1H), 1.58−1.44 (m, 2H), 1.43−1.36 (m, 1H), 1.35−1.23 (m, 3H), 1.23−1.16 (m, 1H), 1.06−0.96 (m, 1H), 0.95 (d, $J$ = 6.4 Hz, 3H), 0.87 (d, $J$ = 6.5 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 164.8, 132.9, 129.4, 128.5, 127.7, 123.8, 83.9, 58.9, 58.3, 54.9, 43.5, 38.5, 37.0, 29.7, 26.8, 21.8, 21.5, 21.4. HRMS (ESI/DART-FTMS): $m/z$ calcd for $C_{20}H_{27}F_3NO_2$ $[M + H]^+$, 370.1994; found, 370.1986.

*5,6-Dichloro-2-((1R,2R,3R,4S)-3-isopropylbicyclo[2.2.1]heptan-2-yl)isoindoline-1,3-dione,* ***25***. To a solution of (−)-**1** (70 mg, 0.46 mmol, 1.0 equiv) in acetic acid (0.7 mL) was added 5,6-dichloroisobenzofuran-1,3-dione (98 mg, 0.46 mmol, 1.0 equiv) at room temperature. The mixture was then stirred at 117 °C using an aluminum heating block for 2 h. The reaction mixture was cooled to room temperature. The solvent was removed under a vacuum, and the residue was purified by prep-HPLC, eluting with 0−90% acetonitrile in water (0.1% TFA) to give **25** (15 mg, 0.04 mmol, 10%) as an off-white solid. $^1$H NMR (400 MHz, chloroform-*d*): $\delta$ 7.89 (s, 2H), 4.07−4.05 (m, 1H), 2.45−2.38 (m, 2H), 2.33 (d, $J$ = 4 Hz, 1H), 1.75−1.52 (m, 3H), 1.51−1.43 (m, 1H), 1.42−1.33 (m, 2H), 1.26−1.19 (m, 1H), 0.94 (d, $J$ = 8 Hz, 3H), 0.70 (d, $J$ = 8 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*): $\delta$ 167.6, 138.8, 131.0, 125.1, 61.3, 46.6, 43.1, 39.9, 35.1, 32.8, 29.6, 23.2, 21.6, 19.6. HRMS (ESI/DART-FTMS): $m/z$ calcd for $C_{18}H_{20}Cl_2NO_2$ $[M + H]^+$, 352.0871; found, 352.0868.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02520.

Renderings of $^1$H NMR and $^{13}$C NMR spectra, summary tables of SFC separation screening results, analytical SFC chromatograms of (+)-**2**, (−)-**2**, (+)-**16**, and (−)-**16**, tables of crystal data and structure refinement for **23** and **25**, tables of bond lengths and angles for **23** and **25**, thermal ellipsoid representations of single crystals **23** and **25**, coordinates and computed total energies for optimized (+)-**1** and (−)-**15** (HCl and free base), and an image of the calculated and experimental VCD and IR spectra for (+)-**1** and (−)-**15** (PDF)

### Accession Codes

CCDC 1983233−1983234 contain 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 336033.

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### Notes

The authors declare no competing financial interest.

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