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Practical Synthesis of (3a*R*, 9b*R*)-8-Fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole: An Advanced Intermediate to Access the RORγt Inverse Agonist BMT-362265

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ABSTRACT: A practical and scalable route to (3a*R*, 9b*R*)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole **10**, an advanced intermediate en route to the synthesis of the RORγt inverse agonist, **BMT-362265**, is described starting from fluorobenzene. The synthesis involved the screening of multiple synthetic routes for their feasibility and scalability. We also demonstrate the utility of an annulating reagent, (*R*)-*N*-(2-chloroethyl)-2-methylpropane-2-sulfinamide, for the diastereoselective synthesis of tricyclic pyrrolidine intermediates **24** and **36** on a multigram scale.

KEYWORDS: *tetralone, RORγt, immunology, heptafluoroisopropyl, vinylsulfone, BMT-362265*

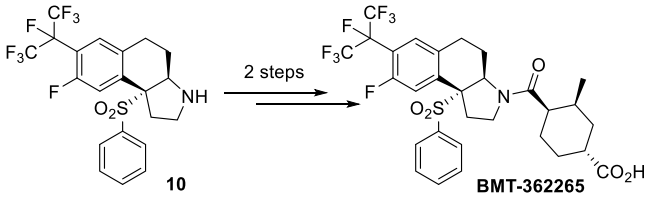
INTRODUCTION

Retinoic acid-related orphan receptors (RORα, RORβ, and RORγ) are members of the nuclear receptor family of transcription factors.[1] RORγt is a splice variant of RORγ and it regulates the expression of proinflammatory cytokines such as interleukin-17 (IL-17).[2] Excessive production of IL-17 has been implicated in several autoimmune disorders such as psoriasis.[3] Preclinical evidence suggests that the use of RORγt inverse agonists leads to reduced production of proinflammatory cytokines such as IL-17. Therefore, inverse agonists of RORγt have the potential for the treatment of a range of immune and inflammatory disorders. In continuation of our research in the same direction,[4,5] we recently reported a novel tricyclic RORγt inverse agonist, **BMT-362265**,[6] which was synthesized via coupling of the tricyclic core **10** with (1*R*, 2*S*, 4*R*)-2-methylcyclohexane-1,4-dicarboxylic acid (Scheme 1). This paper details an inexpensive, safer, and scalable synthetic route to the tricyclic core **10** of **BMT-362265**.

RESULTS AND DISCUSSION

The first-generation synthesis (Scheme 2)[6] of **BMT-362265** was carried out starting from a commercially available 6-iodo-1-tetralone **1**, which was converted to 7-iodo-4-(phenylsulfonyl)-1,2-dihydronaphthalene **3** in two steps with 70% isolated yield. The first step generated a mixture of thioethers **2a** and **2b**, which was oxidized in situ with potassium peroxymonosulfate (oxone) in THF (24 °C, 6 h) to furnish 6-fluoro-7-iodo-4-(phenylsulfonyl)-1,2-dihydronaphthalene **3**. Following that, the tricyclic sulfone core **4** was synthesized in a diastereoselective manner

Scheme 1. Synthesis of BMT-362265 from Advanced Intermediate 10



using the in-house-developed novel annulating reagent[7] (*R*)-*N*-(2-chloroethyl)-2-methylpropane-2-sulfinamide **13** and vinyl sulfone **3** in 65% yield.

Synthesis of (*R*)-*N*-(2-chloroethyl)-2-methylpropane-2-sulfinamide **13** was accomplished via reductive amination of 2-chloroacetaldehyde and (*R*)-2-methylpropane-2-sulfinamide **11** (Scheme 3).[7] Deprotection of Ellman's chiral auxiliary from intermediate **4** using 4 M HCl in 1,4-dioxane and subsequent protection led to the trifluoroacetamide derivative **5** in 87% yield. Installation of the heptafluoroisopropyl moiety was achieved under Ullman's conditions[8] (Cu, heptafluoroisopro-

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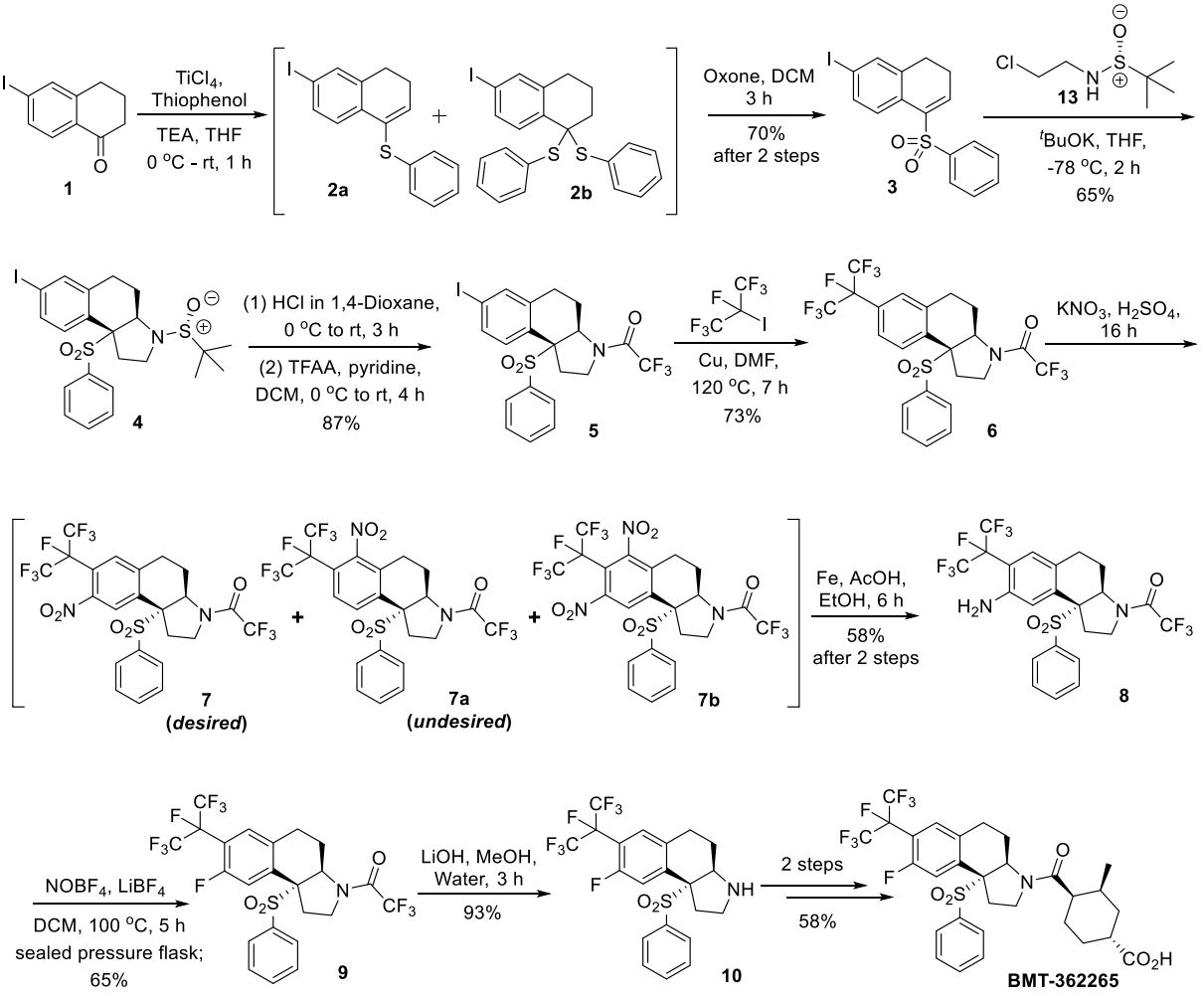
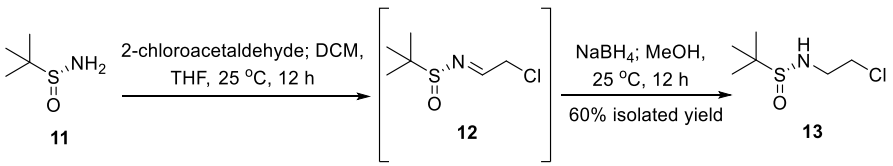
Scheme 2. First-Generation Synthesis of BMT-362265



Scheme 3. Synthesis of (*R*)-*N*-(2-Chloroethyl)-2-methylpropane-2-sulfinamide 13



pyliodide, DMF, 120 °C, and 7 h in a sealed tube) to generate 2,2,2-trifluoro-1-((3a*R*,9b*R*)-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e] indol-3-yl) ethan-1-one **6** in 73% yield. Compound **6** was then subjected to nitration with KNO_3 and H_2SO_4, resulting in a mixture of two regio-isomers (**7**/**7a**) in a ratio of 2.5:1 along with a minor amount (~8%) of dinitro byproduct **7b**. The crude mixture thus obtained was subjected to reduction with iron and acetic acid and the desired amine **8** was isolated in 58% yield. This amine functionality was used as a precursor to install the fluoro moiety employing the Balz−Schiemann reaction,[9] to furnish 8-fluoro-7-(perfluoropropan-2-yl) derivative **9** in 65% yield. Basic hydrolysis of the trifluoroacetamide moiety using LiOH led to the key intermediate **10** in excellent yield (93%).

Although the above scheme could be carried out reasonably well on a small scale, generating multigram quantities of compound **10**, employing this route, posed serious challenges. For example, (i) this synthetic protocol employed 12 linear steps from 6-iodotetralone **1** with an overall yield of only 9.5%; (ii) incorporation of a fluoro moiety via aromatic nitration using the KNO_3/H_2SO_4 mixture resulted in significant safety issues, for example, the potential explosive nature of aromatic nitro derivatives.[10] (iii) due to the exothermic nature of the nitration reaction, control on attenuating overnitration could be challenging and (iv) the nitration reaction led to a mixture of regio-isomers, and (v) the potential for uncontrolled thermal decomposition of aryl diazonium fluoroborate salt, especially when carried out on a large scale (vide infra).[11]

To investigate the safety concern of this reaction, the differential scanning calorimetry (DSC) thermogram was recorded on pure dinitro compound **7b**, which shows a major exotherm at 224 °C with an energy of −1371 J/g (estimated adiabatic temperature increase, ΔT_{ad} = +608 °C) and an onset of a minor exotherm at 102 °C (Figure 1). These data clearly indicate that compound **7b** might not be a safe byproduct of the nitration reaction, when conducted on a larger scale, forcing us

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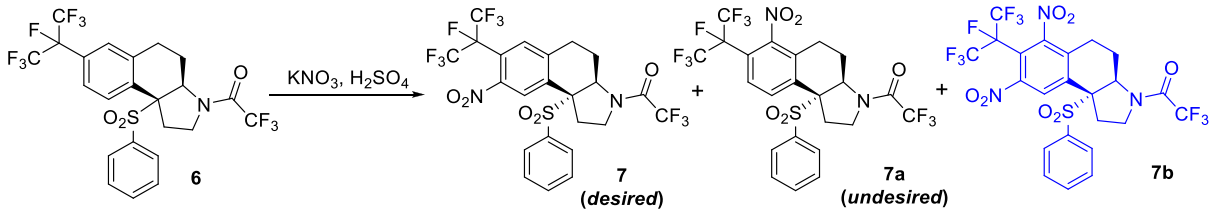


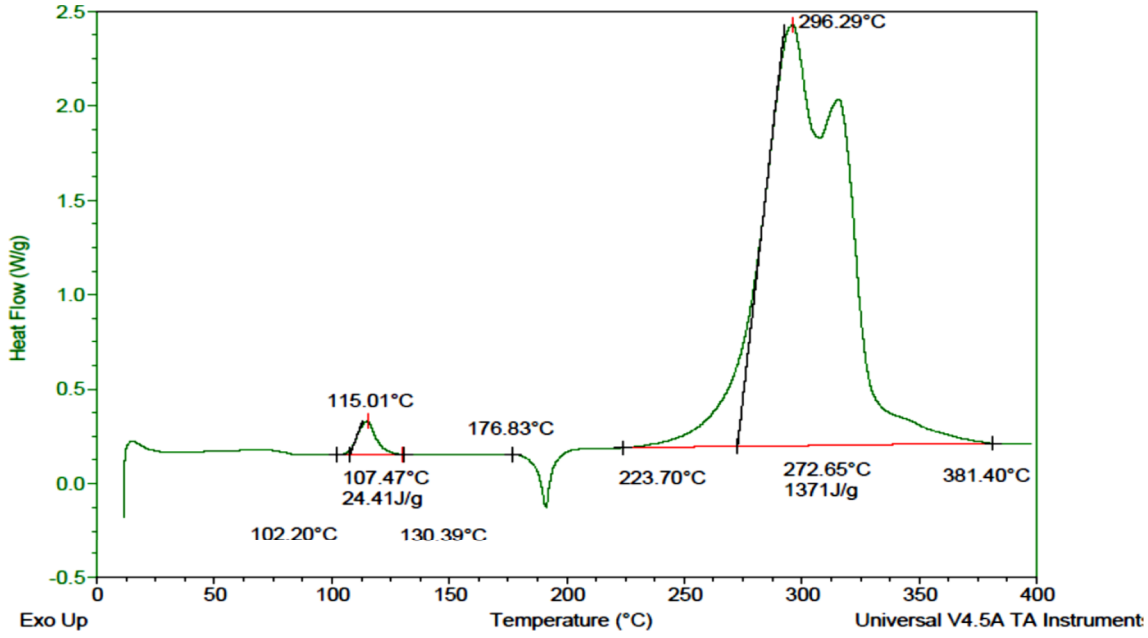
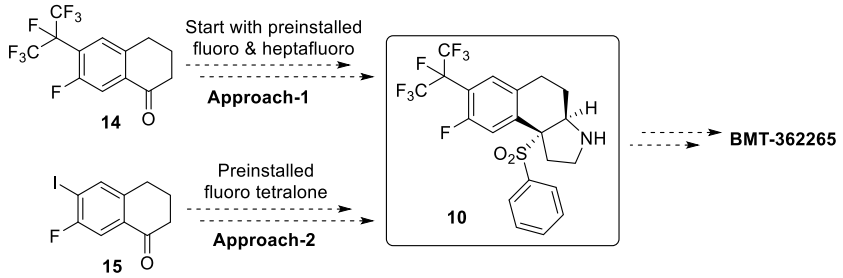


Figure 1. DSC profile of isolated dinitro compound **7b**.

Scheme 4. Alternative Approaches for Synthesis of 10



to explore alternate synthetic routes for the multigram synthesis of key intermediate **10**.

In view of the above challenges, various routes were evaluated. Among these, two approaches were considered for further development (Scheme 4). In approach-1, we intended to start with tetralone **14** wherein the fluoro and heptafluoroisopropyl groups were preinstalled. In parallel, 7-fluoro-6-iodo-1-tetralone **15** (approach-2) was also considered as a potential starting material because conversion of an aryl iodide by Ullmann-type heptafluoroisopropylations is well known in the literature[8] and it was also performed in our laboratory on a multigram scale on several other tricyclic sulfones. It must be mentioned here that though there are literature reports[12] for the synthesis of 7-fluoro-6-bromotetralone, we chose to proceed with 7-fluoro-6-iodo-1-tetralone **15** because our experience with the Ullmann-type heptafluoroisopropylation reaction has been better with iodo than with bromo precursors.

Approach-1. As described in Scheme 4, in this approach, we envisioned to have the fluoro group at the 7-position and the heptafluoroisopropyl moiety at the 6-position. In the forward sense (Scheme 5), 4-fluorobenzaldehyde **16** was treated with *N*-iodosuccinimide (NIS) following a literature procedure[13] to generate the corresponding iodo compound **17** in 80% yield, and Wittig olefination provided olefin **18** in 75% yield. Heptafluoroisopropylation[8] was carried out using perfluoroisopropyl iodide and freshly prepared Cu powder in DMF in a sealed tube at 125 °C for 1 h, resulting in the formation of heptafluoroisopropyl derivative **19** in 70% isolated yield. It is worth mentioning that the quality of heptafluoroisopropyliodide[14] and the freshly prepared Cu powder[15] is crucial for the efficiency of this conversion. Olefin **19** was hydrogenated using a Pd−C catalyst and the ester functionality was hydrolyzed with LiOH in a THF/H_2O (4:1) mixture for 12 h to yield 4-(4-fluoro-3-(perfluoropropan-2-yl)phenyl)butanoic acid **21** in 95% isolated yield. Intramolecular Friedel−Crafts acylation using

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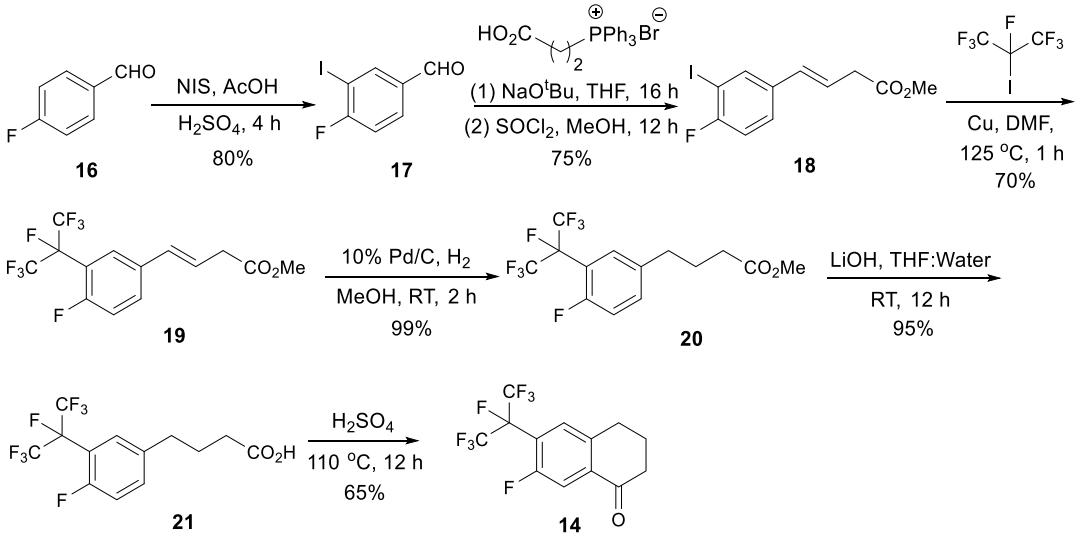
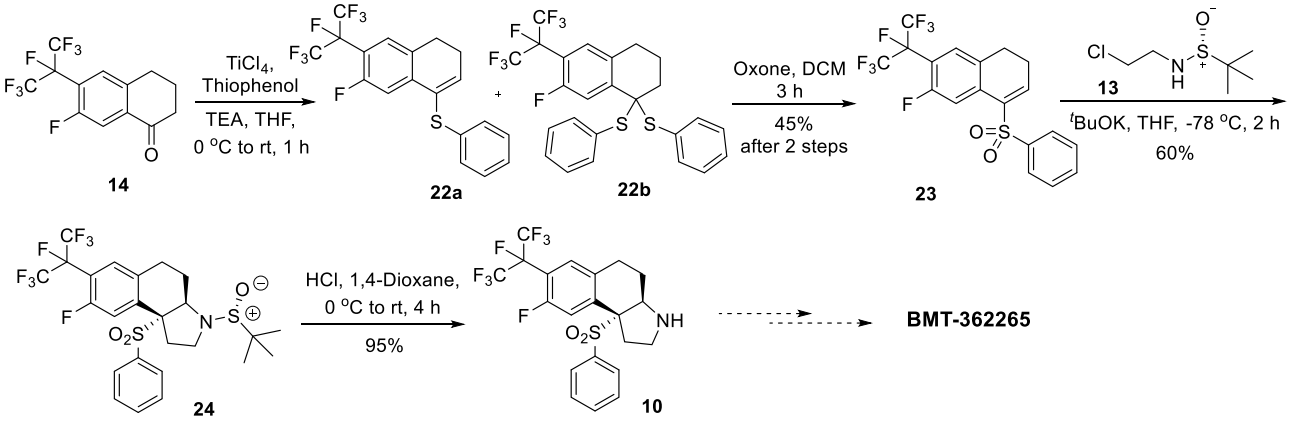
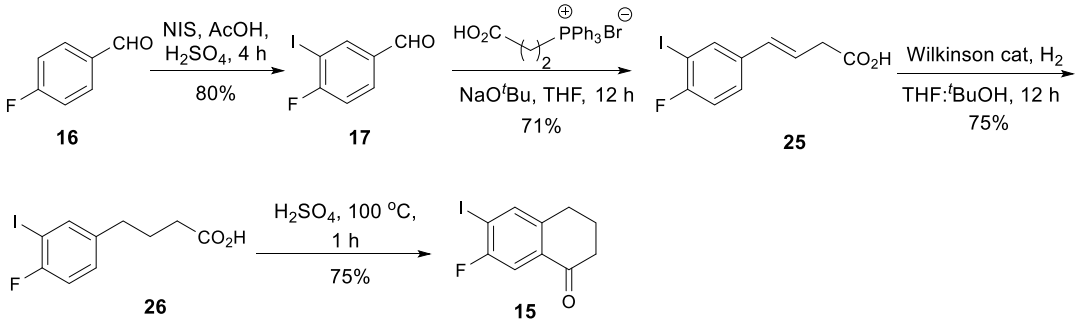
Scheme 5. Synthesis of 7-Fluoro-6-(heptafluoroisopropyl)tetralone 14 from 4-Fluorobenzaldehyde 16



Scheme 6. Synthesis of 10 from 7-Fluoro-6-(heptafluoroisopropyl)tetralone 14



Scheme 7. Synthesis of 7-Fluoro-6-iodo-1-tetralone 15 from 4-Fluorobenzaldehyde 16



H_2SO_4 at 100 °C gave the desired tetralone **14** with high regioselectivity (24:1) and in 65% isolated yield. The observed regioselectivity might be attributed to the steric contribution of the heptafluoroisopropyl group thereby forcing the cyclization to the para position. The overall yield of tetralone **14** over the seven-step sequence depicted in Scheme 5 was 24.6%.

Having tetralone **14** with a preinstalled 7-fluoro functionality in hand, it was subjected to $TiCl_4$-mediated vinylthioether synthesis using thiophenol and triethylamine, which led to a mixture of vinylthioether **22a** and thioketal **22b** as described in Scheme 6. Without further purification, the mixture of **22a** and **22b** was oxidized with potassium peroxymonosulfate to produce vinylsulfone **23** in 45% isolated yield (after two steps) and 15% of unreacted tetralone **14** was recovered. Finally, tricyclic core **24** was synthesized in a stereoselective manner using (*R*)-*N*-(2-chloroethyl)-2-methylpropane-2-sulfinamide **13** under basic conditions (^{t}BuOK) to yield **24** in 60% yield. Deprotection of Ellman's chiral auxiliary was achieved in excellent yield (95%) using HCl in 1,4-dioxane to produce (3a*R*,9b*R*)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5, 9b-hexahydro-1*H*-benzo[e]indole **10** as a white solid.

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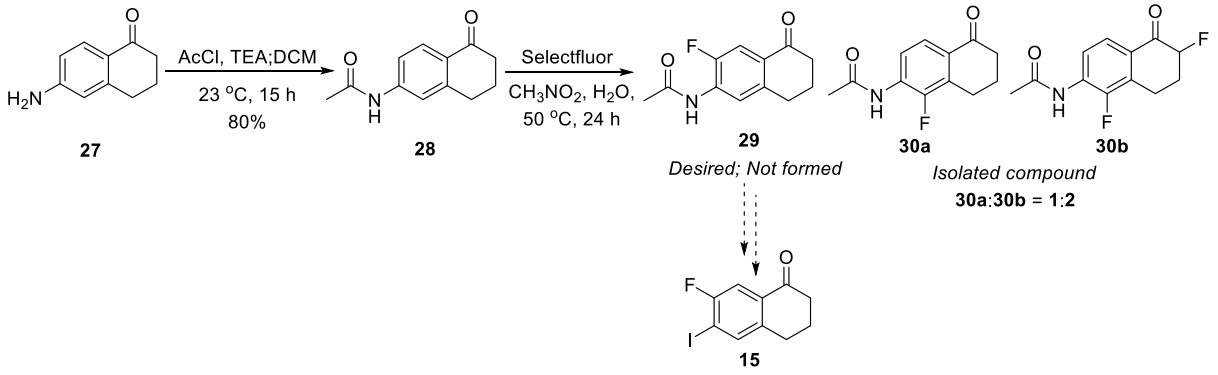
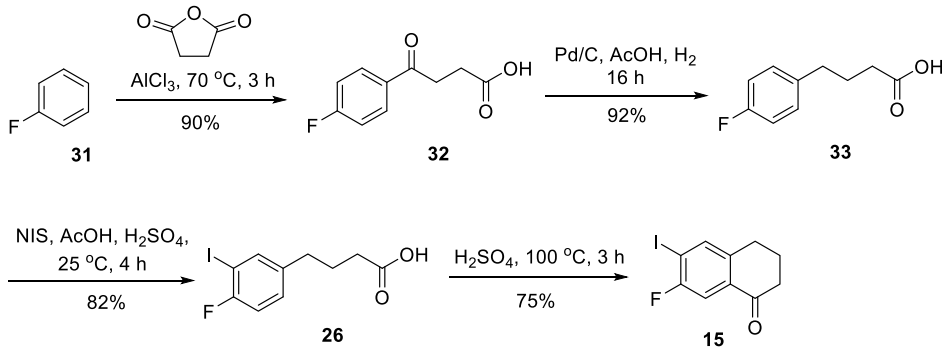
Scheme 8. Synthesis of 7-Fluoro-6-iodo-1-tetralone 15 from 6-Aminotetralone 27



Scheme 9. Synthesis of 7-Fluoro-6-iodo-1-tetralone 15 from Fluorobenzene 31



Although the new synthesis approach (Scheme 6) was reasonably successful to access the tricyclic core **10**, it suffered mainly from two drawbacks, viz., (i) conversion of tetralone **14** to vinylsulfone **23**, followed by cyclization resulted in moderate conversion of 45 and 60%, respectively, and (ii) it involved a total of 11 steps from 4-fluorobenzaldehyde **16** with an overall yield of 6.3%, compared to the first-generation medicinal chemistry approach of a total of 10 steps and 9.5% overall yield. Hence, this approach did not offer any significant advantage, other than being more convergent in terms of having preinstalled heptafluoro and fluoro moieties and mitigating the safety issues concerned with nitration and the Balz−Schiemann reaction in the original scheme.

Approach-2. The limitations of approach-1 as outlined above led us to explore the second approach to tetralone **15**, which is discussed in Schemes 7−9. The routes were designed and executed to pick the best one in terms of cost, safety, scalability, and overall yields. As mentioned earlier, in this approach, we decided to synthesize 7-fluoro-6-iodo-1-tetralone **15** and install the perfluoro moiety later in the sequence. Literature search revealed the commercial availability of tetralone **15**, but the sources were limited and quite expensive from the scalability point of view. Therefore, it was decided to synthesize the compound in-house from readily available and inexpensive 4-fluorobenzaldehyde (Scheme 7).

The Wittig olefination of intermediate **17** with (2-carboxyethyl) triphenylphosphonium bromide gave (*E*)-4-(4-fluoro-3-iodophenyl)but-3-enoic acid **25** in 71% isolated yield. Selective hydrogenation of the olefin, using Wilkinson's catalyst,[16] provided 4-(4-fluoro-3-iodophenyl)butanoic acid **26** in 75% yield. Our attempts to hydrogenate the olefin using either Pd−C or PtO_2 provided the desired compound **26** in low yield (20−25%) with the des-iodo compound being the major (50−60%) product. Due to the presence of a bulkier iodo group, intramolecular Friedel−Crafts acylation on compound **26** using sulfuric acid favored the regioselective (22:1) formation of tetralone **15** in 75% yield. Though this scheme involved only four steps with a good overall yield of 32%, the main concern was the use of the Wilkinson catalyst, which was found to be expensive for scalability.

In parallel, we decided to attempt amide-assisted metal-free direct fluorination[17] on commercially available and inexpensive 6-aminotetralone **27** to access tetralone **15** (Scheme 8). Though we were aware of the possibility of formation of other regioisomers, the plan was to screen the reaction conditions for the installation of fluorine at position 7 of the tetralone core using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor). However, when 6-acetamidotetralone **28** was treated with the same in aqueous nitromethane, it did not result in the desired fluorination product **29**, instead a mixture of undesired tetralones **30a** and **30b** was isolated in a ratio of 1:2.

Finally, the synthesis of 7-fluoro-6-iodo-1-tetralone **15** (Scheme 9) was accomplished starting with cheap and commercially available fluorobenzene **31**, which on Friedel−Crafts acylation with succinic anhydride catalyzed by $AlCl_3$ at 70 °C for 3 h yielded 4-(4-fluorophenyl)-4-oxobutanoic acid **32** in 90% yield. Reduction of the benzylic carbonyl group was achieved under hydrogenation conditions (Pd−C, AcOH, H_2, 16 h) to produce 4-(4-fluorophenyl)butanoic acid **33** in 92% yield.[18] Iodination of **33** using NIS resulted 82% yield of 4-(4-fluoro-3-iodophenyl)butanoic acid **26**, which underwent Friedel−Crafts acylation under acidic conditions to generate 7-fluoro-6-iodo-1-tetralone **15**. Following this route, the title compound **15** was synthesized in 46.5% overall yield in four steps and was scaled up to >250 g.

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Scheme 10. Synthesis of (3a*R*,9b*R*)-8-Fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole 10 from 7-Fluoro 6-Iodo Tetralone 15

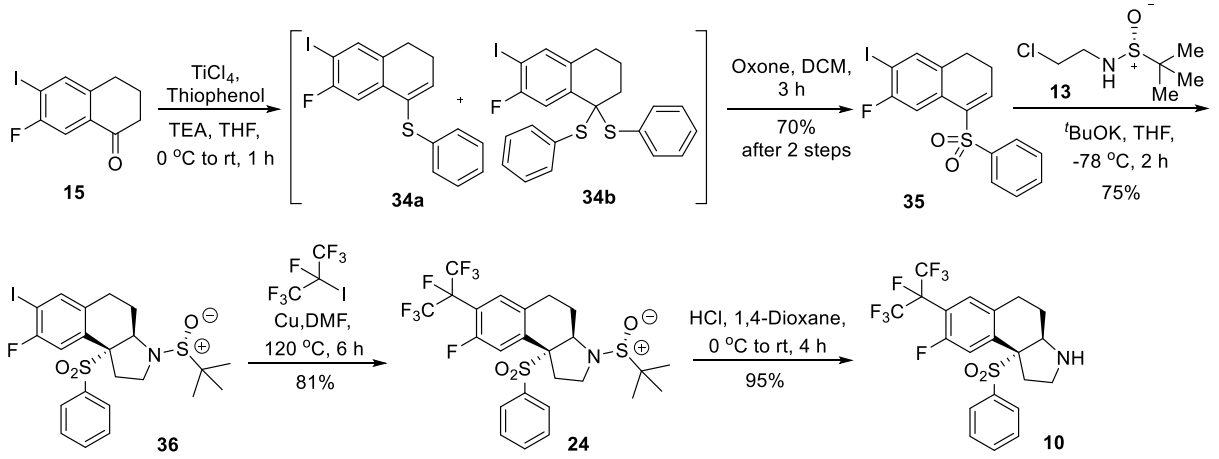
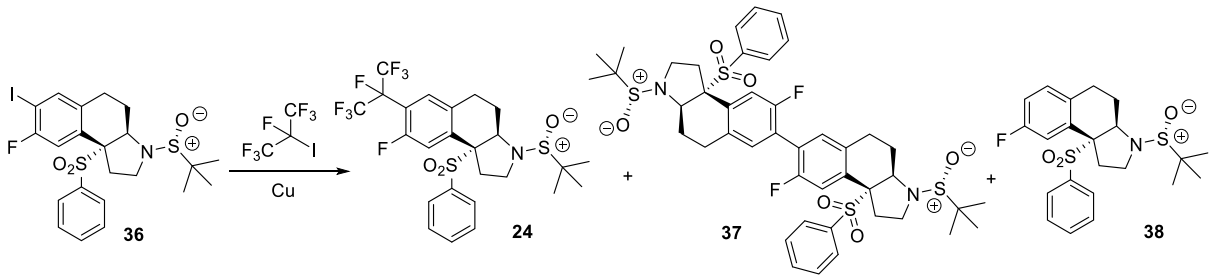


Table 1. Optimization of Ullmann-Type Heptafluoroisopropylations for the Synthesis of 24[a]



entries	36 (g)	perfluoroisopropyliodide (equiv)	solvent; temp	time (h)	24 (%)[b]	36/37/38 (%)[b]
1	0.2	1.5	DMF; 120 °C	6	12	62% of **36**
2	0.2	1.5	DMF; 120 °C	12	12	50% of **36**
3	0.2	1.5	DMF; 100 °C	6	no reaction[c]	
4	0.2	1.5	DMF; 110 °C	6	no reaction[c]	
5	0.2	1.5	DMSO; 100 °C	6	no reaction[c]	
6	0.2	1.5	DMSO; 110 °C	6	no reaction[c]	
7[d]	0.2	1.5	DMSO; 120 °C	6	17% of **38**	
8	0.2	2.5	DMF; 120 °C	6	75	11% of **37**
9[d]	0.2	2.5	DMF; 130 °C	6	19	21% of **38**
10	5	2.5	DMF; 120 °C	6	80[e]	<2% of **37**
11	20	2.5	DMF; 120 °C	6	81[e]	<2% of **37**

[a]Heptafluoroisopropylation was performed using heptafluoroisopropyliodide and freshly prepared Cu powder in a sealed tube. [b]Reaction was monitored by LCMS. [c]Product formation was not observed, only unreacted **36**. [d]Multiple peaks were observed in LCMS. [e]Isolated yield.

Compared to other reaction sequences discussed above (Schemes 7 and 8), the protocol outlined in Scheme 9 met the criteria of scalability, safety, and commercial viability and was employed for the synthesis of **10**.

The synthesis of key intermediate **10** from tetralone **15** is outlined in Scheme 10. Tetralone **15** was subjected to $TiCl_4$-mediated vinylthioether formation using thiophenol and triethylamine in tetrahydrofuran resulting in a mixture of vinylthioether **34a** and thioketal **34b**, which was subjected to oxidation under two different conditions, *viz.* potassium peroxymonosulfate and *m*CPBA. Though both the conditions gave the vinylsulfone **35** in similar yields (70−75% over two steps), the reaction with potassium peroxymonosulfate was preferred because of a shorter reaction time (3 h) and an easy work-up procedure compared to the *m*CPBA reaction (12 h). The formation of tricyclic core **36** was accomplished in a stereoselective manner using (*R*)-*N*-(2-chloroethyl)-2-methylpropane-2-sulfinamide **13** under basic conditions in 75% yield.

Compound **36**, when subjected to Ullman coupling (Table 1) using heptafluoroisopropyliodide (1.5 equiv), freshly prepared copper, and DMF at 120 °C for 6 h, gave only 12% yield of product **24** along with 62% unreacted **36** (entry 1). Prolonged reaction times (12 h) did not improve the yield of product **24** (entry 2). Further reaction optimization was carried out by varying the solvent, reaction temperature, and equivalence of reactants as summarized in entries 3−11 in Table 1. The results revealed that lowering of reaction temperature below 120 °C (entry 3 and 4) did not result in any product formation. Also, changing the solvent from DMF to DMSO (entries 5 and 6) did not improve the reaction outcome. However, at elevated temperature (120 °C) in DMSO (entry 7), it resulted an unclean reaction with formation of 17% of des-iodo compound **38**. Higher equivalents (2.5 equiv) of heptafluoroisopropylio-

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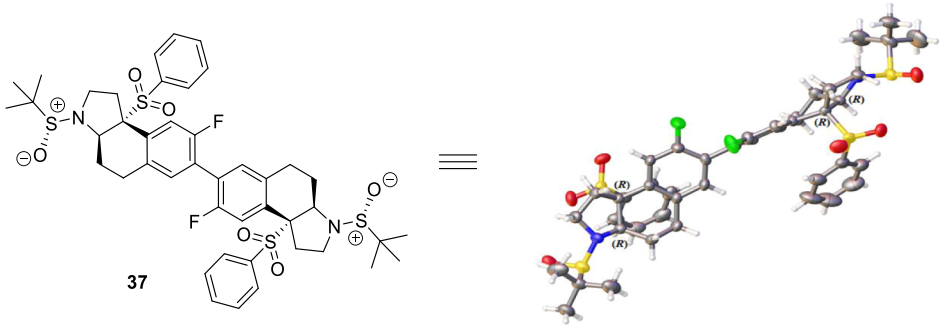

Figure 2. Single-crystal XRD of dimer byproduct **37** (CCDC 2042178).

dide were found to be a key factor in improving the yield (75% isolated) for this conversion (entry 8), along with 11% of homocoupled byproduct **37**, which was confirmed by single crystal X-ray analysis (Figure 2). However, a further increase in temperature to 130 °C under similar reaction conditions (entry 9) resulted in the formation of multiple products—only 19% of the desired compound **36** along with 21% of des-iodo compound **38** was observed in the reaction mixture. Based on the conditions used for screening, conditions in entry 8 were considered as superior and were applied to check the reproducibility on higher scales (a 5 g scale in entry 10 and a 20 g scale in entry 11). Both cases resulted in >80% isolated yield of compound **24** with a negligible amount (1−2%) of dimer **37**. The enriched selectivity may have been achieved during scale up, due to better deoxygenation under argon purging (with a higher flow rate) potentially leading to a reduced oxygen level in the reaction mixture. Deprotection of Ellman's chiral auxiliary was achieved in almost quantitative yield (>95%) using HCl in 1,4-dioxane to produce the target compound (3a*R*,9b*R*)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole **10**.

Through this optimized second-generation sequence, advanced intermediate **10** was synthesized in an overall isolated yield of 40.4% over five steps from tetralone **15**. However, to access compound **10** in multikilogram quantities, further optimization would be desirable for the step involving heptafluoroisopropylation.

■ CONCLUSIONS

In summary, a safe, cost-effective, robust, and scalable route was developed for the synthesis of the key intermediate (3a*R*,9b*R*)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexa hydro-1*H*-benzo[e]indole **10**, en route to the synthesis of the RORγt inverse agonist **BMT-362265**. The newly developed synthetic sequence utilized readily available starting materials and circumvented the safety concerns related to both the nitration reaction and the introduction of the fluoro moiety by the Balz−Schiemann reaction. The first-generation route consists of 10 steps with 9.5% overall yield from 6-iodo-1-tetralone **1**. This modified route allowed us to synthesize the title compound **10** on a multigram scale with 40.4% overall yield in five steps starting from in-house-synthesized 7-fluoro-6-iodo-1-tetralone **15**, which was synthesized in more than 200 g yield starting from fluorobenzene.

■ EXPERIMENTAL SECTION

Commercially available reagents were used without additional purification, unless otherwise stated. Thin layer chromatography was carried out using plates coated with Kieselgel 60F254. For purification in column chromatography, a CombiFlash NextGen System and RediSep media (silica) columns were used. Characterization of the isolated products was carried out in $CDCl_3$ or DMSO-d_6 at T = 300 K. Chemical shifts are reported relative to the solvent residual value δ = 7.26 ($CDCl_3$) and 2.50 (DMSO-d_6) for ^{1}H NMR and δ = 77.16 ($CDCl_3$) and 39.52 (DMSO-d_6) for ^{13}C NMR. The NMR spectra were recorded on 300, 400, and 500 MHz spectrometers for ^{1}H and on 75, 100, and 125 MHz spectrometers for ^{13}C at T = 300 K. The spectra were referenced against the internal NMR solvent standard. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dspt (doublet of septate), m (multiplet), and so forth. In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). The LCMS mass spectra were recorded on an Agilent 1200 series spectrometer connected with an Agilent 6140 quadruple MS instrument. Accurate mass measurements (HRMS) were performed on an Accela UHPLC system, hyphenated with an LTQ-Orbitrap XL mass spectrometer (Thermo Scientific) in the electrospray (ESI) mode. Specific optical rotation (SOR) values were measured on a RUDOLPH Autopol V automatic polarimeter. Melting points were recorded using a BUCHI M-560 instrument.

4-Fluoro-3-iodobenzaldehyde (17). This compound was synthesized in 80% isolated yield from 4-fluorobenzaldehyde **16** following the literature protocol.[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 8.36−8.29 (m, 1H), 7.92−7.86 (m, 1H), 7.23 (t, J = 8.6 Hz, 1H). Analytical data comply with the previously reported data in the literature.[19]

Methyl (*E*)-4-(4-Fluoro-3-iodophenyl)but-3-enoate (18). To a solution of 4-fluoro-3-iodobenzaldehyde **17** (5 g, 20 mmol) and (2-carboxyethyl)triphenylphosphonium bromide (10 g, 30 mmol) in tetrahydrofuran (80 mL) at −78 °C was added sodium-*t*-butoxide (5 g, 52 mmol) in portions over a period of 30 min. The reaction mixture was warmed to room temperature and stirred for 16 h. After completion, THF was removed under reduced pressure and the residue was taken in water (50 mL) and washed with dichloromethane (2 × 50 mL). The pH of the aqueous layer was adjusted to ∼2 by slow addition of conc. HCl, which was extracted with diethyl ether (2 × 50 mL). The combined ether layer was dried over anhydrous sodium sulfate and concentrated. The crude was purified by column chromatography on the silica gel using a mixture of petroleum ether and ethyl acetate (v/v = 1/5) to afford (*E*)-4-(4-fluoro-3-iodophenyl)but-3-enoic acid (30 g) as a pale yellow liquid, which was taken in methanol (50 mL) and cooled to 0 °C. Thionyl chloride (1.6 mL, 22 mmol) was added dropwise to the solution over a period of 10 min and stirring was continued for 12 h at room temperature. All volatiles were removed under

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reduced pressure and the resulting residue was dissolved in dichloromethane (50 mL) and washed with saturated sodium bicarbonate solution (2 × 50 mL), followed by brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to yield methyl-(*E*)-4-(4-fluoro-3-iodophenyl)-but-3-enoate **18** (4.8 g, 15 mmol, 75% yield) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, J = 6.0, 2.0 Hz, 1H), 7.30 (ddd, J = 8.4, 4.9, 2.3 Hz, 1H), 7.00 (t, J = 8.5 Hz, 1H), 6.39 (d, J = 16.6 Hz, 1H), 6.23 (td, J = 16.1, 7.0 Hz, 1H), 3.73 (s, 3H), 3.25 (dd, J = 7.3, 1.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.74, 161.12 (d, J = 246.5 Hz, 1C), 136.94 (d, J = 2.2 Hz, 1C), 134.91 (d, J = 3.7 Hz, 1C), 130.93, 127.87 (d, J = 7.3 Hz, 1C), 122.83 (d, J = 2.9 Hz, 1C), 115.58 (d, J = 24.2 Hz, 1C), 81.47 (d, J = 26.4 Hz, 1C), 52.04, 38.02. ^{19}F NMR (376 MHz, $CDCl_3$): δ −95.69 (s, 1F). LCMS (ESI) m/z: $[M - H]^+$ calcd for $C_{11}H_{10}FIO_2$, 319.1; found, 319.0.

Methyl (*E*)-4-(4-Fluoro-3-(perfluoropropan-2-yl)-phenyl)but-3-enoate (19). In a 25 mL sealed tube, methyl (*E*)-4-(4-fluoro-3-iodophenyl)but-3-enoate **18** (4 g, 12.5 mmol) was dissolved in dimethylformamide (30 mL) and the mixture was degassed with nitrogen for 15 min. Freshly prepared copper powder[15] (1.068 g, 16.81 mmol) and 1,1,1,2,3,3,3-heptafluoro-2-iodopropane[14] (8 mL, 56.2 mmol) were added and the tube was sealed properly. The reaction mixture was heated at 125 °C for 1 h. On completion, the tube was brought to room temperature. All the volatiles were evaporated and the residue was dissolved in ethyl acetate (50 mL) and washed with ammonium chloride solution (25 mL), water (25 mL), and brine (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification of the crude mixture was performed by silica gel column chromatography (eluted with 10% ethyl acetate in petroleum ether) to provide methyl (*E*)-4-(4-fluoro-3-(perfluoropropan-2-yl)phenyl)but-3-enoate **19** (3.1 g, 70.1% yield) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64−7.46 (m, 2H), 7.16 (dd, J = 9.0, 11.0 Hz, 1H), 6.55−6.44 (m, 1H), 6.39−6.21 (m, 1H), 3.74 (s, 3H), 3.28 (d, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.68, 158.74 (dd, J = 255.8, 5.1 Hz, 1C), 133.91 (t, J = 2.9 Hz, 1C), 131.30, 130.74 (d, J = 8.7 Hz, 1C), 126.12 (br d, J = 15.3 Hz, 1C), 123.72 (d, J = 2.2 Hz, 1C), 120.49 (dq, J = 287.4, 28.0 Hz, 2C), 117.64 (d, J = 23.3 Hz, 1C), 114.83 (dd, J = 21.8, 13.1 Hz, 1C), 91.69 (dspt, J = 202.0, 42.1 Hz, 1C), 52.12, 38.05. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.21 (dd, J = 18.0, 6.9 Hz, 6F), −110.70 (spt, J = 18.0 Hz, 1F), −178.01 (s, 1F). LCMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{10}F_8O_2$, 363.0; found, 363.0.

Preparation of Cu Powder.[15] To a solution of $CuSO_4 \cdot 5H_2O$ (400 g) in water (1500 mL) under ice cold conditions and continuous stirring was added Zn powder (140 g) in equal portions (10 × 14 g; due to exothermicity) over a period of 30 min. Stirring was continued at room temperature (24 °C) till disappearance of the blue color (∼30 min). After complete settlement of the solids, a clear supernatant was decanted out and the precipitate was allowed to stir with aqueous 1.5 N HCl solution (1500 mL). After completion of effervescence, stirring was stopped and solids were permitted to settle for ∼10 min. The supernatant liquid was removed by decantation to generate brownish solids, which was washed multiple times with water (4 × 1000 mL) and decanted until the pH of the washed liquid became neutral (pH 7). Final washing was performed with methanol (500 mL), followed by filtration. Solids were dried under reduced pressure to generate brown solids of copper (100 g, 98% yield).

Methyl 4-(4-Fluoro-3-(perfluoropropan-2-yl)phenyl)-butanoate (20). To a solution of methyl (*E*)-4-(4-fluoro-3-(perfluoropropan-2-yl)phenyl)but-3-enoate **19** (2 g, 5.45 mmol) in methanol (20 mL) was added 10% Pd−C (200 mg, 0.03 mmol) and stirred at 25 °C under a hydrogen atmosphere (bladder) for 2 h. The reaction mixture was passed through a Celite bed (3 cm) and washed with methanol (2 × 20 mL). The combined filtrate was concentrated in vacuum to yield methyl 4-(4-fluoro-3-(perfluoropropan-2-yl)phenyl)butanoate **20** (1.92 g, 99% yield) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (br d, J = 7.0 Hz, 1H), 7.39−7.34 (m, 1H), 7.14 (dd, J = 8.3, 11.3 Hz, 1H), 3.70 (s, 3H), 2.72 (t, J = 8.0 Hz, 2H), 2.37 (t, J = 7.3 Hz, 2H), 1.98 (quin, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.63, 158.02 (dd, J = 252.9, 5.1 Hz, 1C), 138.07 (t, J = 3.6 Hz, 1C), 133.31 (d, J = 8.7 Hz, 1C), 127.90 (br d, J = 15.3 Hz, 1C), 120.55 (dq, J = 286.9, 27.2 Hz, 2C), 117.64 (d, J = 23.4 Hz, 1C), 114.39 (dd, J = 21.8, 12.4 Hz, 1C), 91.69 (dspt, J = 202.0, 42.1 Hz, 1C), 51.64, 34.38, 33.18, 26.44. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.31 (dd, J = 5.4, 17.7 Hz, 6F), −113.26 (spt, J = 19.1 Hz, 1F), −177.99 (br s, 1F). LCMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}F_8O_2$, 365.0; found, 365.0.

4-(4-Fluoro-3-(perfluoropropan-2-yl)phenyl)butanoic Acid (21). Lithium hydroxide (0.631 g, 26.4 mmol) was added to a solution of methyl 4-(4-fluoro-3-(perfluoropropan-2-yl)phenyl)butanoate **20** (4.8 g, 13.18 mmol) in THF (50 mL) and water (10 mL) at 25 °C and stirred for 12 h. Tetrahydrofuran was evaporated under reduced pressure and the residue was diluted with water (20 mL) and acidified with aqueous 2 N HCl solution to pH ∼ 3. The aqueous part was extracted with dichloromethane (2 × 50 mL). The combined dichloromethane layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated to give 4-(4-fluoro-3-(perfluoropropan-2-yl)phenyl)butanoic acid **21** (4.4 g, 95% yield) as a pale yellow gummy oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 7.0 Hz, 1H), 7.39−7.32 (m, 1H), 7.13 (dd, J = 8.5, 11.3 Hz, 1H), 2.73 (t, J = 7.8 Hz, 2H), 2.41 (t, J = 7.3 Hz, 2H), 1.98 (quin, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.04, 158.06 (dd, J = 252.9, 4.4 Hz, 1C), 137.87, 133.32 (br d, J = 8.7 Hz, 1C), 127.90 (br d, J = 14.5 Hz, 1C), 120.55 (dq, J = 286.9, 27.2 Hz, 2C), 117.37 (br d, J = 22.5 Hz, 1C), 114.48 (dd, J = 21.8, 12.4 Hz, 1C), 91.69 (dspt, J = 202.0, 42.1 Hz, 1C), 34.29, 33.15, 26.18. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.27 (dd, J = 17.7, 6.8 Hz, 6F), −113.06 (spt, J = 17.7 Hz, 1F), −177.96 (br s, 1F). LCMS (ESI) m/z: $[M - H]^+$ calcd for $C_{13}H_{10}F_8O_2$, 349.2; found, 349.1.

7-Fluoro-6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one (14). In a 100 mL round-bottomed flask, a solution of 4-(4-fluoro-3-(perfluoropropan-2-yl)phenyl) butanoic acid **21** (2.8 g, 8 mmol) in neat H_2SO_4 (29.8 mL, 560 mmol) was heated to 110 °C for 12 h. The reaction mixture was quenched very slowly (over 30 min) with ice and extracted with methyl-*tert*-butyl ether (4 × 25 mL). The combined organic layer was washed with water (50 mL) and brine (50 mL) and concentrated to generate the crude product, which was purified by flash chromatography (40 g silica gel column) using 5−30% ethyl acetate in petroleum ether to produce 7-fluoro-6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one **14** (1.72 g, 65% yield) as a colorless thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 11.2 Hz, 1H), 7.56 (d, J = 6.4 Hz, 1H), 3.03 (t, J = 6.0 Hz, 2H), 2.72 (t, J = 6.0 Hz, 2H), 2.21 (quin, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.03 (d, J = 1.7 Hz, 1C), 158.01 (dd, J = 255.0, 4.6 Hz, 1C), 140.12 (d, J = 2.5 Hz, 1C), 140.17−140.05 (m, 1C), 140.32−136.39 (m, 1C),

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129.14 (d, J = 15.8 Hz, 1C), 119.25 (dd, J = 22.0, 13.7 Hz, 1C), 124.62−115.77 (m, 1C), 115.30−115.19 (m, 1C), 115.02, 38.46, 28.88, 22.88. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.0 (dd, J = 6.1, 18.4 Hz, 6F), −111.01, −111.24 (m, 1F), −177.41 (br s, 1F). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_8F_8O$, 333.0526; found, 333.0516.

6-Fluoro-7-(perfluoropropan-2-yl)-4-(phenylsulfonyl)-1,2-dihydronaphthalene (23). To a solution of 7-fluoro-6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-1(2*H*)-one **14** (600 mg, 1.806 mmol) in THF (10 mL) at 0 °C was added $TiCl_4$ (1.0 M in DCM) (3.252 mL, 3.252 mmol) and was stirred for 15 min. The reaction mixture was slowly brought to −10 °C and to that was added a solution of benzenethiol (0.332 mL, 3.252 mmol) in THF (4 mL) dropwise, followed by triethylamine (0.50 mL, 3.612 mmol) at the same temperature. The reaction mixture was allowed to reach room temperature and stirring was continued for another 40 min. It was quenched with water (20 mL). THF was evaporated and the remaining aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layer was dried on sodium sulfate, filtered, and concentrated to provide a crude mixture (1 g) of (7-fluoro-6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-1-yl)(phenyl)-sulfane **22a** and (7-fluoro-6-(perfluoropropan-2-yl)-1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(phenylsulfane) **22b**. The crude mixture thus obtained was dissolved in dichloromethane (20 mL), cooled to 0 °C and *m*CPBA (1.16 g, 4.71 mmol), and stirred for 12 h. After completion, it was washed with saturated aqueous sodium bicarbonate solution (2 × 25 mL). The organic layer was dried over sodium sulfate and concentrated to generate 1.2 g of the crude semisolid product. Purification of the as-obtained product by column chromatography (using a 24 g silica column, eluted with 20% ethyl acetate in hexanes) produced a colorless gummy liquid of 6-fluoro-7-(perfluoropropan-2-yl)-4-(phenylsulfonyl)-1,2-dihydronaphthalene **23** (370 mg, 0.81 mmol, 45% after two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−7.95 (m, 2H), 7.79 (d, J = 13.2 Hz, 1H), 7.66−7.54 (m, 4H), 7.36 (d, J = 7.6 Hz, 1H), 2.83 (t, J = 8.0 Hz, 2H), 2.68−2.63 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.05 (dd, J = 4.5, 252.5 Hz, 1C), 143.93, 139.82, 138.41, 133.69, 132.14 (t, J = 2.7 Hz, 1C), 132.04 (d, J = 9.1 Hz, 1C), 129.45 (2C), 127.64 (2C), 127.01 (br d, J = 15.4 Hz, 1C), 120.40 (q, J = 286.4 Hz, 1C), 120.17 (q, J = 287.0 Hz, 1C), 114.10, 113.88, 91.39 (dspt, J = 204.4, 34.5, 1C), 26.28, 23.46. ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.15 (dd, J = 17.6, 6.8 Hz, 6F), −109.74 (spt, J = 17.6 Hz, 1F), −178.17. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{12}F_8O_2S$, 457.0509; found, 457.0505.

(3a*R*,9b*R*)-3-((*S*)-*tert*-Butylsulfinyl)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenyl sulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]-indole (24). 6-Fluoro-7-(perfluoropropan-2-yl)-4-(phenylsulfonyl)-1,2-dihydronaphthalene **23** (370 mg, 0.81 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. To that was added (*R*)-*N*-(2-chloroethyl)-2-methylpropane-2-sulfinamide **13** (297 mg, 1.62 mmol) and stirred for 15 min. A separately prepared solution of potassium-*t*-butoxide (364 mg, 3.24 mmol) in THF (5 mL) was added slowly to the reaction mixture at −78 °C over a period of 25 min and stirred for 2 h at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine solution (25 mL), dried over sodium sulfate, filtered, and concentrated under vacuum to dryness. It was purified by flash chromatography (using 12 g silica column, eluted with 40−50% ethyl acetate/hexanes) to afford (3a*R*,9b*R*)-3-((*S*)-*tert*-butylsulfinyl)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]-indole **24** (293 mg, 0.48 mmol, 60% yield) as a white solid. mp 181.0−181.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.59 (m, 1H), 7.46−7.37 (m, 5H), 7.26−7.22 (m, 1H), 4.48−4.44 (m, 1H), 3.92−3.87 (m 1H), 3.03−2.98 (m, 1H), 2.72−2.66 (m, 2H), 2.42−2.37 (m, 1H), 2.22−2.09 (m, 1H), 1.98−1.94 (m, 1H), 1.94−1.60 (m, 1H), 1.16 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_d): δ 156.31 (dd, J = 4.7, 250.3 Hz, 1C), 137.75 (t, J = 2.9 Hz, 1C), 137.46 (d, J = 8.7 Hz, 1C), 134.85, 134.74, 129.67 (2C), 129.02 (2C), 127.13 (br d, J = 15.3 Hz, 1C), 119.17, 118.93, 120.10 (q, J = 286.0 Hz, 1C), 119.82 (q, J = 287.0 Hz, 1C), 112.77 (dd, J = 12.7, 22.2 Hz, 1C), 91.19 (dspt, J = 207.1, 36.3, 1C), 73.92, 63.79, 56.75, 35.93, 27.41, 24.19, 22.71 (3C). ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.72, −75.99 (m, 6F), −111.12, −111.17 (m, 1F), −178.19 (br s, 1F). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{25}F_8NO_3S_2$, 604.1236; found, 604.1240. SOR $[\alpha]_D^{25}$ (c 0.1, MeOH): −20.0.

(3a*R*,9b*R*)-8-Fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]-indole (10). In a 50 mL round-bottomed flask, (3a*R*,9b*R*)-3-((*S*)-*tert*-butylsulfinyl)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e] indole **24** (150 mg, 0.25 mmol) was taken in 10 mL of 1,4-dioxane, cooled to 0 °C, and added with commercial 4 M HCl in 1,4-dioxane solution (3 mL) dropwise. The reaction mixture was slowly brought to room temperature over a period of 1 h and stirring was continued for another 3 h. After completion, the mixture was concentrated and purified by supercritical fluid chromatography to achieve white solids of (3a*R*,9b*R*)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e] indole **10** (118 mg, 0.236 mmol, 95% yield). mp 163.0−163.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72−7.69 (m, 1H), 7.47−7.39 (m, 3H), 7.36−7.28 (m, 3H), 4.00−3.91 (m 1H), 3.04−2.84 (m, 3H), 2.70−2.55 (m, 1H), 2.33−2.20 (m, 1H), 2.06−1.96 (m, 1H), 1.88−1.73 (m, 1H), 1.31−1.16 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.26 (dd, J = 250.0, 5.1 Hz, 1C), 139.95 (d, J = 8.0 Hz, 1C), 138.53 (t, J = 2.5 Hz, 1C), 135.16, 134.46 (2C), 129.65 (2C), 128.75 (2C), 126.57 (br d, J = 14.5 Hz, 1C), 121.42 (d, J = 27.7 Hz, 1C), 119.82 (d, J = 24.4 Hz, 1C), 118.57 (d, J = 24.0 Hz, 1C), 112.14 (dd, J = 22.2, 12.7 Hz, 1C), 76.92, 60.07, 45.63, 38.18, 27.75, 25.86. ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.72, −75.99 (m, 6F), −113.39, −114.07 (m, 1F), −177.37 (br s, 1F). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{17}F_8NO_2S$, 500.0931; found, 500.0926. SOR $[\alpha]_D^{25}$ (c 0.1, MeOH): −230.0.

(*E*)-4-(4-Fluoro-3-iodophenyl)but-3-enoic Acid (25). To a solution of 4-fluoro-3-iodobenzaldehyde **17** (25 g, 100 mmol) and (2-carboxyethyl)-triphenylphosphonium bromide (50 g, 149 mmol) in tetrahydrofuran (400 mL) at −78 °C was portionwise added sodium-*t*-butoxide (25 g, 260 mmol) over a period of 30 min, and the mixture was stirred for 16 h at room temperature. After completion, THF was removed and the residue was dissolved in water (100 mL), followed by washing with dichloromethane (2 × 75 mL). The pH of the aqueous layer was adjusted to ∼2 by slow addition of concentrated HCl and extracted with diethyl ether (2 × 200 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. It was purified by silica column using a mixture of petroleum ether and ethyl acetate (v/v = 1/5) as an eluent to afford the desired (*E*)-4-(4-fluoro-3-iodophenyl)but-3-enoic acid **25** (21.8 g, 71% yield) as a pale yellow gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.37 (br s, 1H), 7.89 (dd, J =

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2.0, 6.0 Hz, 1H), 7.53−7.40 (m, 1H), 7.21 (t, J = 8.3 Hz, 1H), 6.52−6.40 (m, 1H), 6.38−6.18 (m, 1H), 3.18 (d, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.40, 160.39 (d, J = 242.0 Hz, 1C), 136.43, 135.25, 129.73, 127.83 (d, J = 7.2 Hz, 1C), 124.43 (d, J = 2.8 Hz, 1C), 115.73 (d, J = 24.8 Hz, 1C), 82.46 (d, J = 25.8 Hz, 1C), 37.74. ^{19}F NMR (376 MHz, DMSO-d_6): δ −97.29 (s, 1F). LCMS (ESI) m/z: $[M - H]^+$ calcd for $C_{10}H_8FIO_2$, 304.9; found, 304.8.

4-(4-Fluoro-3-iodophenyl)butanoic Acid (26). In a 100 mL autoclave, a solution of (*E*)-4-(4-fluoro-3-iodophenyl)but-3-enoic acid **25** (400 mg, 1.307 mmol) and tris-(triphenylphosphine) rhodium(I) chloride (100 mg, 0.108 mmol) in tetrahydrofuran (5 mL) and *tert*-butyl alcohol (10 mL) was stirred at 25 °C under a hydrogen atmosphere (bladder) for 12 h. The reaction mixture was passed through a Celite bed (2 cm) and washed with THF/^{t}BuOH (1:1, 20 mL). The combined filtrate was concentrated in vacuum and the residue was purified by silica-gel column chromatography (eluted with 30% ethyl acetate in petroleum ether) to afford 4-(4-fluoro-3-iodophenyl)butanoic acid **26** (302 mg, 75% yield) as a colorless gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1H), 7.66−7.64 (m, 1H), 7.24−7.21 (m, 1H), 7.17−7.13 (m, 1H), 2.57−2.53 (m, 2H), 2.25−2.18 (m, 2H), 1.80−1.73 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 174.10, 159.59 (d, J = 238.7 Hz, 1C), 139.95 (d, J = 3.2 Hz, 1C), 138.66 (d, J = 1.4 Hz, 1C), 130.26 (d, J = 7.2 Hz, 1C), 115.35 (d, J = 23.6 Hz, 1C), 81.78 (d, J = 25.4 Hz, 1C), 32.95, 32.89, 26.17. ^{19}F NMR (376 MHz, DMSO-d_6): δ −99.57. HRMS (ESI) m/z: $[M - H]^+$ calcd for $C_{10}H_{10}FIO_2$, 306.9631; found, 307.0276.

7-Fluoro-6-iodo-3,4-dihydronaphthalen-1(2*H*)-one (15). A mixture of 4-(4-fluoro-3-iodophenyl)butanoic acid **26** (280 mg, 0.91 mmol) and sulfuric acid (5 mL) was taken in a round-bottomed flask at room temperature and was heated at 70 °C for 2 h. It was brought to room temperature and poured very slowly into ice water (15 mL) under vigorous stirring. The solids formed were filtered, washed with water (2 × 15 mL), and dried under reduced pressure. They were purified by silica gel column chromatography (using dichloromethane as an eluent) to afford 7-fluoro-6-iodo-3,4-dihydronaphthalen-1(2*H*)-one **15** (197 mg, 75% yield) as a light yellow solid. mp 112.1−112.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, J = 6.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 2.90−2.87 (m, 2H), 2.60−2.57 (m, 2H), 2.04−1.98 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.82, 160.43 (d, J = 240.7 Hz, 1C), 142.68 (d, J = 3.2 Hz, 1C), 140.57, 134.38 (d, J = 5.2 Hz, 1C), 112.01 (d, J = 24.3 Hz, 1C), 90.64 (d, J = 26.2 Hz, 1C), 38.45, 28.03, 23.03. ^{19}F NMR (376 MHz, DMSO-d_6): δ −97.90. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_8FIO$, 290.9682; found, 290.9687.

***N*-(5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-acetamide (28).** 6-Amino-3,4-dihydronaphthalen-1(2*H*)-one **27** (11 g, 68.2 mmol) was taken in dichloromethane (200 mL) and to it was added triethylamine (14.27 mL, 102 mmol) at 0 °C. Acetyl chloride (5.82 mL, 82 mmol) was added dropwise and the reaction mass was stirred at 24 °C for 16 h. The reaction was quenched with water (150 mL). The organic layer was separated, washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The crude material was purified by column chromatography (eluted with 20−25% ethyl acetate in petroleum ether) to achieve pale brown solids of *N*-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide **28** (11.1 g, 54.56 mmol, 80% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.62−7.60 (m, 1H), 7.47 (dd, J = 8.5, 2.0 Hz, 1H), 2.89 (t, J = 6.0 Hz, 2H), 2.58−2.53 (m, 2H), 2.07 (s, 3H), 2.01 (m, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.18, 168.93, 145.86, 143.66, 127.62, 127.30, 117.55, 116.85, 38.41, 29.28, 24.19, 22.89. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}NO_2$: 204.1025, found, 204.1013. Analytical data comply with the previously reported data in the literature.[20]

***N*-(1-Fluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (30a) and *N*-(1,6-Difluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (30b).** *N*-(5-Oxo-5,6,7,8-tetrahydro naphthalen-2-yl)acetamide **28** (5 g, 24.60 mmol) was taken in nitromethane (20 mL) and water (20 mL) and to that 1-(chloromethyl)-4-fluoro-1,4 diazabicyclo[2.2.2] octane-1,4-diiumtetrafluoroborate (Selectfluor) (8.72 g, 24.60 mmol) was added and the reaction mixture was heated at 50 °C for 15 h. Another lot of Selectfluor (8.72 g, 24.60 mmol) was then added and the reaction was continued to stir at 50 °C for 12 h. The reaction was quenched by adding 20 mL water and the nitromethane layer was separated. The aqueous layer was re-extracted with dichloromethane (2 × 20 mL) and combined with the nitromethane layer. The organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (eluted with 10−15% ethyl acetate in petroleum ether) to produce white solids of *N*-(1-fluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide **30a** (1.33 g, 6.02 mmol, 24.5% yield) and *N*-(1,6-difluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide **30b** (3.05 g, 12.8 mmol, 52% yield) as off-white solids. (a) Analytical data of *N*-(1-fluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide **30a**: mp 135.1−135.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H), 8.06 (t, J = 8.1 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 2.91 (t, J = 6.1 Hz, 2H), 2.60−2.53 (m, 2H), 2.15 (s, 3H), 2.12−1.98 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.70, 169.26, 149.08 (d, J = 242.6 Hz, 1C), 131.34 (d, J = 16.0 Hz, 1C), 130.97 (d, J = 11.7 Hz, 1C), 128.35, 122.40 (d, J = 3.5 Hz, 1C), 119.80, 37.90, 23.82, 21.92, 21.41. ^{19}F NMR (376 MHz, DMSO-d_6): δ −130.04. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}FNO_2$, 222.0930; found, 222.0926. (b) Analytical data of *N*-(1,6-difluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide **30b**: mp 160.0−160.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (t, J = 8.0 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 5.22−5.02 (m, 1H), 3.26 (dd, J = 4.0, 17.6 Hz, 1H), 2.94 (ddd, J = 17.3, 12.0, 4.8 Hz, 1H), 2.65−2.41 (m, 1H), 2.39−2.29 (m, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.30 (dd, J = 15.2, 3.0 Hz, 1C), 168.69, 148.14 (d, J = 241.2 Hz, 1C), 131.62 (d, J = 10.1 Hz, 1C), 129.30 (d, J = 16.9 Hz, 1C), 127.09, 124.40, 119.37, 90.41 (d, J = 186.5 Hz, 1C), 28.95 (d, J = 19.7 Hz, 1C), 24.76, 19.78 (dd, J = 11.5, 4.3 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ −135.43, −191.26. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{11}F_2NO_2$, 240.0836; found, 240.0815.

4-(4-Fluorophenyl)-4-oxobutanoic Acid (32). To a solution of succinic anhydride (100 g, 999 mmol), fluorobenzene **31** (192 g, 1999 mmol) in 1,2-dichloroethane (750 mL) at 0 °C was added aluminum chloride (266 g, 1999 mmol) in portions over 30 min. It was heated at 70 °C for 3 h. On completion, it was cooled to 0 °C and slowly added into a precooled aqueous 5 N HCl solution (300 mL). After stirring for 15 min, the layers separated and the aqueous layer was further extracted with dichloromethane (2 × 100 mL). The combined organic layer was washed with water (2 × 250 mL) and brine (2 × 200 mL), dried over sodium sulfate, and concentrated. The resulting crude material was stirred with petroleum ether (300 mL) and filtered to afford 4-(4-fluorophenyl)-4-oxobutanoic acid **32** (175.3 g, 894 mmol, 90%) as a pale yellow solid. mp

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102.5−103.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (br s, 1H), 8.09−8.04 (m, 2H), 7.38−7.32 (m, 2H), 3.26 (t, J = 6.20 Hz, 2H), 2.59 (t, J = 6.20 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.08, 173.73, 164.98 (d, J = 249.9 Hz, 1C), 133.18 (d, J = 3.0 Hz, 1C), 130.79 (d, J = 9.4 Hz, 2C), 115.66 (d, J = 21.8 Hz, 2C), 33.03, 27.82. ^{19}F NMR (376 MHz, DMSO-d_6): δ −106.16. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_9FO_3$, 197.0614; found, 197.0611.

4-(4-Fluorophenyl)butanoic Acid (33). A mixture of (4-fluorophenyl)-4-oxobutanoic acid **32** (100 g, 510 mmol) and acetic acid (1000 mL) was taken in a 5 L autoclave and the solution was deoxygenated by purging nitrogen gas over 25 min. Pd−C (54.2 g) was then added in portions (five portions; 10 min interval). The mixture was stirred at room temperature under 140 psi hydrogen pressure for 16 h. The mixture was filtered through Celite and washed with methanol (3 × 200 mL). The filtrate was concentrated in vacuum to afford 4-(4-fluorophenyl)butanoic acid **33** (85.2 g, 468 mmol, 92% yield) as a light brown liquid. mp 38.8−39.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1H), 7.24−7.20 (m, 2H), 7.11−7.07 (m, 2H), 2.60−2.56 (m, 2H), 2.24−2.20 (m, 2H), 1.83−1.77 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.65, 161.11 (d, J = 239.7 Hz, 1C), 138.09 (d, J = 2.9 Hz, 1C), 130.44 (d, J = 7.8 Hz, 2C), 115.36 (d, J = 20.9 Hz, 2C), 33.97, 33.42, 26.81. ^{19}F NMR (376 MHz, DMSO-d_6): δ −117.58. HRMS (ESI) m/z: [M − H]$^+$ calcd for $C_{10}H_{11}FO_2$, 181.1864; found, 181.1559.

4-(4-Fluoro-3-iodophenyl)butanoic Acid (26). A mixture of 4-(4-fluorophenyl)butanoic acid **33** (80 g, 439 mmol), acetic acid (600 mL), and NIS (89 g, 395 mmol) was taken in a 1.5 L round-bottomed flask and cooled to 0 °C. To that H_2SO_4 (250 mL) was added slowly and stirred for 4 h. After completion, the reaction mixture was poured slowly into an ice water mixture under vigorous stirring. The resulting solid precipitates were filtered and washed with water and dried under vacuum. The crude product thus obtained was purified by silica column chromatography (eluted with 30% ethyl acetate in petroleum ether) to afford 4-(4-fluoro-3-iodophenyl)butanoic acid **26** (100 g, 324 mmol, 82% yield) as a colorless thick gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1H), 7.66−7.64 (m, 1H), 7.24−7.21 (m, 1H), 7.17−7.13 (m, 1H), 2.57−2.53 (m, 2H), 2.25−2.18 (m, 2H), 1.80−1.73 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 174.10, 159.59 (d, J = 238.7 Hz, 1C), 139.95 (d, J = 3.2 Hz, 1C), 138.66 (d, J = 1.4 Hz, 1C), 130.26 (d, J = 7.2 Hz, 1C), 115.35 (d, J = 23.6 Hz, 1C), 81.78 (d, J = 25.4 Hz, 1C), 32.95, 32.89, 26.17. ^{19}F NMR (376 MHz, DMSO-d_6): δ −99.57. HRMS (ESI) m/z: [M − H]$^+$ calcd for $C_{10}H_{10}FIO_2$, 306.9631; found, 307.0276.

7-Fluoro-6-iodo-3,4-dihydronaphthalen-1(2*H*)-one (15). Synthesized following the same protocol as explained previously. 4-(4-Fluoro-3-iodophenyl)butanoic acid **26** (70 g, 227 mmol) resulted in 7-fluoro-6-iodo-3,4-dihydronaphthalen-1(2*H*)-one **15** (49.4 g, 75% yield) as a light yellow solid.

6-Fluoro-7-iodo-4-(phenylsulfonyl)-1,2-dihydronaphthalene (35). To a 5000 mL four-neck round-bottomed flask containing a solution of 7-fluoro-6-iodo-3,4-dihydronaphthalen-1(2*H*)-one **15** (150 g, 517 mmol) in THF (1500 mL), $TiCl_4$ solution (1 M in CH_2Cl_2) (830 mL, 830 mmol) was added dropwise for 45 min at 0 °C. After complete addition, a solution of thiophenol (84.4 mL, 830 mmol) in THF (300 mL) was added dropwise, followed by triethylamine (216 mL, 1.55 mol) while keeping the reaction temperature below <10 °C. The reaction mixture was slowly brought to room temperature (24 °C) and stirred for 1 h. It was quenched with water (500 mL) and the organic layer was separated. The aqueous layer was re-extracted with diethyl ether (3 × 250 mL). The organic layers were combined, washed with brine solution (500 mL), separated and dried over sodium sulfate, filtered, and concentrated to a crude mixture of (7-fluoro-6-iodo-3,4-dihydronaphthalen-1-yl)(phenyl)sulfane **34a** and (7-fluoro-6-iodo-1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(phenylsulfane) **34b** (1:1, 220 g) as a brown oil. The crude mixture thus obtained was taken in a 2500 mL single-neck round-bottom flask and dissolved in DMF (1500 mL). To that potassium peroxymonosulfate (483 g, 784.5 mmol) was added and stirred overnight. After 16 h, it was quenched with water (500 mL) and the aqueous layer was extracted with diethyl ether (3 × 500 mL) and the organic layers were combined, washed with water (2 × 500 mL) and brine (250 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified through a silica column (eluted with 0−20% ethyl acetate in a hexane mixture) to obtain 6-fluoro-7-iodo-4-(phenylsulfonyl)-1,2-dihydronaphthalene **35** (152 g, 366.4 mmol, 70% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95−7.92 (m, 2H), 7.70−7.28 (m, 6H), 2.75−2.70 (m, 2H), 2.60−2.54 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.65 (d, J = 238.9 Hz, 1C), 144.44, 139.55, 138.35, 136.67, 134.29 (d, J = 3.6 Hz, 1C), 133.88, 129.71 (2C), 128.44 (d, J = 8.2 Hz, 1C), 127.10 (2C), 110.80 (d, J = 27.2 Hz, 1C), 82.07 (d, J = 25.4 Hz, 1C), 24.85, 22.99. ^{19}F NMR (376 MHz, $CDCl_3$): δ −95.42. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{16}H_{12}FIO_2S$, 414.9665; found, 414.9657.

(3a*R*,9b*R*)-3-((*S*)-*tert*-Butylsulfinyl)-8-fluoro-7-iodo-9b-(phenylsulfonyl)-2,3,3a,4,5, 9b-hexahydro-1*H*-benzo[e]indole (36). In a 10 L two-neck round-bottom flask fitted with a mechanical stirrer, 6-fluoro-7-iodo-4-(phenylsulfonyl)-1,2-dihydronaphthalene **35** (150 g, 362.1 mmol) was dissolved in THF (1500 mL) and cooled to −78 °C. (*R*)-*N*-(2-Chloroethyl)-2-methylpropane-2-sulfinamide **13** (133 g, 724.8 mmol) was added at −78 °C and stirred for 10 min. A separately prepared solution of potassium-*t*-butoxide (162.4 g, 1.45 mol) in THF (2500 mL) was added slowly to the reaction mixture and stirred for 2 h at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution (1500 mL) and extracted with ethyl acetate (3 × 1000 mL). The organic layers were combined, washed with brine (1500 mL), dried over sodium sulfate, filtered, and concentrated under vacuum. The crude compound was purified through a silica column (eluted with 40−50% ethyl acetate/hexanes mixture) to afford (3a*R*,9b*R*)-3-((*S*)-*tert*-butylsulfinyl)-8-fluoro-7-iodo-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole **36** (153 g, 271.6 mmol, 75% yield) as a white solid. mp 196.8−197.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77−7.72 (m, 1H), 7.64−7.45 (m, 5H), 7.20 (d, J = 12.8 Hz, 1H), 4.32−4.21 (m, 1H), 3.73−3.52 (m, 2H), 3.39−3.15 (m, 2H), 2.72−2.55 (m, 1H), 2.15−2.01 (m, 1H), 1.87−1.76 (m, 1H), 1.62−1.49 (m, 1H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.32 (d, J = 238.5 Hz, 1C), 138.33, 138.04 (d, J = 3.2 Hz, 1C), 134.94, 134.71 (t, J = 23.8 Hz, 1C), 132.27 (d, J = 6.7 Hz, 1C), 129.82 (2C), 129.18, 128.99 (d, J = 9.2 Hz, 2C), 116.59 (d, J = 25.5 Hz, 1C), 83.14 (d, J = 25.6 Hz, 1C), 73.04, 63.20, 56.70, 36.21, 26.45, 23.26, 22.45 (3C). ^{19}F NMR (376 MHz, DMSO-d_6): δ −98.52, −100.17, −115.76. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{25}FINO_3S_2$, 562.0383; found, 562.0293. SOR $[\alpha]_D^{25}$ (c 0.1, MeOH): +10.0.

(3a*R*,9b*R*)-3-((*S*)-*tert*-Butylsulfinyl)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenyl sulfonyl)-2,3,3a,4,5,9b-

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hexahydro-1*H*-benzo[e]indole (24). In a 1000 mL sealed tube, (3a*R*,9b*R*)-3-((*S*)-*tert*-butylsulfinyl)-8-fluoro-7-iodo-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexa hydro-1*H*-benzo[e]indole **36** (11 g, 19 mmol) was taken in DMF (250 mL) and degassed with argon gas for 10 min. To that were added freshly prepared copper powder (18.1 g, 285 mmol) and 1,1,1,2,3,3,3-heptafluoro-2-iodopropane (12.2 mL, 85.3 mmol). The reaction mixture was then heated at 120 °C for 6 h. On completion, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to generate a gummy liquid of the crude product. The crude was taken in ethyl acetate (100 mL) and washed with 100 mL of water, followed by 75 mL brine. The combined organic layer was dried over sodium sulfate and concentrated under vacuum. It was purified by column chromatography using a 240 g silica column, eluted with 25% ethyl acetate in hexanes to produce light yellow solids of (3a*R*,9b*R*)-3-((*S*)-*tert*-butylsulfinyl)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3, 3a,4,5,9b-hexahydro-1*H*-benzo[e]-indole **24** (9.6 g, 15.92 mmol, 81% yield). (a) Analytical data of compound **24** were captured previously. (b) Analytical data of (3a*R*, 3′a*R*, 9b*R*, 9′b*R*)-3-((*R*)-*tert*-butylsulfinyl)-3′-(*tert*-butylsulfinyl)-8,8′-difluoro-9b,9′b-bis-(phenylsulfonyl)-2,2′,3,3a,3′,3′a,4,4′,5,5′,9b,9′b-dodecahydro-1*H*,1′*H*-7,7′-bibenzo[e]indole **37**: mp 185.3−185.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (t, J = 7.5 Hz, 2H), 7.58 (d, J = 7.5 Hz, 4H), 7.51−7.42 (m, 4H), 7.39−7.31 (m, 2H), 7.07 (t, J = 5.0 Hz, 2H), 4.47 (dd, J = 4.3, 6.8 Hz, 2H), 3.97−3.83 (m, 2H), 2.99 (td, J = 12.9, 8.6 Hz, 2H), 2.78−2.59 (m, 4H), 2.43 (td, J = 12.5, 4.5 Hz, 2H), 2.31−2.21 (m, 2H), 2.03 (ddd, J = 13.3, 8.8, 4.0 Hz, 2H), 1.73−1.64 (m, 2H), 1.18 (s, 18H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.83. ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.88 (d, J = 248.0 Hz, 2C), 135.82 (2C), 135.61 (2C), 134.29 (2C), 132.32 (t, J = 3.6 Hz, 2C), 130.86 (2C), 130.35 (4C), 128.80 (4C), 123.31−123.03 (m, 2C), 117.57−117.26 (m, 2C), 73.46 (2C), 63.73 (2C), 57.49 (2C), 40.13 (2C), 36.87 (2C), 26.89 (2C), 24.47 (2C), 23.42 (6C). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{44}H_{50}F_2N_2O_6S_4$, 869.2598; found, 869.2602. SOR $[\alpha]_D^{25}$ (c 0.1, MeOH): +45.60. (c) Analytical data of (3a*R*,9b*R*)-3-((*S*)-*tert*-Butylsulfinyl)-8-fluoro-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]-indole **38**: mp 185.3−185.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−7.58 (m, 1H), 7.53−7.47 (m, 2H), 7.46−7.39 (m, 2H), 7.25 (d, J = 10.0 Hz, 1H), 7.05−6.93 (m, 2H), 4.47 (dd, J = 7.5, 4.5 Hz, 1H), 3.90 (ddd, J = 10.4, 8.2, 4.0 Hz, 1H), 3.00 (td, J = 12.8, 8.4 Hz, 1H), 2.72−2.55 (m, 2H), 2.45−2.35 (m, 1H), 2.22−2.08 (m, 1H), 1.94 (td, J = 9.0, 4.5 Hz, 1H), 1.68−1.59 (m, 1H), 1.17 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.15 (s, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.07 (d, J = 244.3 Hz, 1C), 135.89, 135.73 (d, J = 3.6 Hz, 1C), 134.23, 132.30 (d, J = 7.3 Hz, 1C), 130.40 (2C), 129.72 (d, J = 7.3 Hz, 1C), 128.79 (2C), 117.00 (d, J = 22.7 Hz, 1C), 115.96 (d, J = 20.9 Hz, 1C), 73.63, 63.87, 57.57, 40.23, 36.86, 27.06, 24.58, 23.54 (3C). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}FNO_3S_2$, 436.1416; found, 436.1419. SOR $[\alpha]_D^{25}$ (c 0.1, MeOH): −52.40.

(3a*R*,9b*R*)-8-Fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]-indole (10). It was synthesized following the same protocol as explained previously. (3a*R*,9b*R*)-3-((*S*)-*tert*-Butylsulfinyl)-8-fluoro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e] indole **24** (75 g, 124.4 mmol) resulted in (3a*R*,9b*R*)-8-fluoro-7-(per fluoropropan-2-yl)-9b-(phenylsulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]-indole **10** (59 g, 118.3 mmol, 95% yield) as white solids.

Nitration of 2,2,2-Trifluoro-1-((3a*R*,9b*R*)-7-(perfluoropropan-2-yl)-9b-(phenyl sulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e]indol-3-yl)ethan-1-one (6). To a precooled mixture (0 °C) of 2,2,2-trifluoro-1-((3a*R*,9b*R*)-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e]indol-3-yl)ethan-1-one **6** (500 mg, 0.86 mmol) in conc. sulfuric acid (0.08 ml, 1.47 mmol) was added potassium nitrate (0.79 mg, 0.079 mmol). The reaction mixture was then stirred for 16 h at room temperature. After completion, the reaction was quenched by the slow addition of cold water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to achieve a crude regioisomeric mixture of nitro compounds (720 mg; **7**, **7a**, and **7b**). All compounds were purified by preparative HPLC to achieve light yellow solids of desired 2,2,2-trifluoro-1-((3a*R*,9b*R*)-8-nitro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e]indol-3-yl) ethan-1-one **7** (295 mg, 0.47 mmol, 55% yield); 2,2,2-trifluoro-1-((3a*R*,9b*R*)-6-nitro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e] indol-3-yl)ethan-1-one **7a** (107 mg, 0.17 mmol, 20% yield); and 1-((3a*R*,9b*R*)-6,8-dinitro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e]indol-3-yl)-2,2,2-trifluoroethan-1-one **7b** (34 mg, 0.052 mmol, 6% yield). (a) Analytical data of 2,2,2-trifluoro-1-((3a*R*,9b*R*)-8-nitro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e]indol-3-yl)ethan-1-one **7**: mp 163.3−163.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.53−7.48 (m, 3H), 7.37 (d, J = 7.6 Hz, 2H), 4.86−4.81 (m, 1H), 3.97−3.82 (m, 2H), 3.51−3.40 (m, 1H), 2.92−2.82 (m, 2H), 2.37−2.33 (m, 1H), 1.97−1.89 (m, 1H), 1.54−1.50 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 154.31 (q, J = 38.2 Hz, 1C), 147.38, 143.53, 137.50, 135.16, 134.01, 129.46 (3C), 129.38 (2C), 126.50, 119.67 (br q, J = 286.1 Hz, 1C), 119.45 (br q, J = 287.9 Hz, 1C), 115.77 (q, J = 287.9 Hz, 1C), 115.17, 115.01, 73.33, 60.56, 44.80, 32.74, 26.55, 24.01. ^{19}F NMR (376 MHz, DMSO-d_6): δ −71.43 (s, 1F), −74.15, −74.62 (m, 6F), −183.67 (br s, 1F). LCMS (ESI) m/z: $[M + 18]^+$ calcd for $C_{23}H_{16}F_{10}N_2O_5S$: 640.0; found: 640.0. HRMS (ESI) m/z: $[(M + H)-(COCF_3)^\bullet]$ calcd for $C_{23}H_{16}F_{10}N_2O_5S$, 527.0876; found, 527.0884. SOR $[\alpha]_D^{25}$ (c 0.1, MeOH): −30.40. (b) Analytical data of 1-((3a*R*,9b*R*)-6,8-dinitro-7-(perfluoropropan-2-yl)-9b-(phenylsulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e] indol-3-yl)-2,2,2-trifluoroethan-1-one **7b**: mp 196.0−196.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 8.06−7.94 (m, 2H), 7.88 (t, J = 8.0 Hz, 1H), 7.60 (s, 1H), 4.93 (dd, J = 12.0, 5.2 Hz, 1H), 3.95−3.90 (m, 2H), 3.49−3.41 (m, 1H), 2.95−2.86 (m, 2H), 2.44−2.39 (m, 1H), 2.34−2.25 (m, 1H), 1.58−1.48 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.28 (q, J = 36.3 Hz, 1C), 147.76, 147.22 (d, J = 3.6 Hz, 1C), 143.86, 136.81, 135.26 (d, J = 12.4 Hz, 1C), 131.75, 129.58, 126.78, 126.50, 124.35, 119.60 (br q, J = 284.1 Hz, 1C), 119.33 (br q, J = 287.0 Hz, 1C), 115.35 (d, J = 19.6 Hz, 1C), 116.22 (q, J = 287.7 Hz, 1C), 91.09 (dspt, J = 215.8, 34.9 Hz, 1C), 74.02, 60.22, 44.71 (br q, J = 3.6 Hz, 1C), 33.09, 26.62, 24.12. ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.44 (s, 1F), −74.52, −74.88 (m, 6F), −183.28 (br s, 1F). LCMS (ESI) m/z: $[M + 18]^+$ calcd for $C_{23}H_{15}F_{10}N_3O_7S$, 685.0; found, 685.0. HRMS (ESI) m/z: $[(M + H)-(COCF_3)^\bullet]$ calcd for $C_{23}H_{15}F_{10}N_3O_7S$, 572.0726; found, 572.0742. SOR $[\alpha]_D^{25}$ (c 0.1, MeOH): −6.0.

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■ ASSOCIATED CONTENT

Supporting Information

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NMR spectra (^{1}H, ^{13}C, and ^{19}F), SOR, and XRD details of compound **37** (PDF)

Crystal structure data and refinement details of compound **37** (CCDC 2042178) (CIF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This research publication is dedicated to the memory of Dr. Ramakanth Sarabu, who inspired all of us in many ways.

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