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Process Development on an Efficient New Convergent Formal Synthesis of MIV-150

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Abstract:

Starting from a known linear route and a proposed convergent route, we have successfully developed a new hybrid convergent route to MIV-150 that takes advantage of the robust chemistry for the preparation of a fluoroketal and the stereospecific Negishi coupling of an iodocyclopropane moiety to a benzene ring. Stereoselective *β*- and *cis*-iodination chemistry was developed for the preparation of an enantiomerically pure iodocyclopropanecarboxylate. Following the Negishi coupling, proven chemistry from the linear route was incorporated, thus ensuring a similar high-purity profile for the final active pharmaceutical ingredient (API). In addition, we have prepared and evaluated a series of basic inorganic and organic MIV-150 salts that have drastically increased water solubility over the parent compound.

Introduction

The identification of human immunodeficiency virus type-1 (HIV-1) as the causative agent of acquired immunodeficiency syndrome (AIDS) has prompted an intense research effort to find effective therapies for this devastating disease.[1] Current understanding of the events in HIV proliferation proposes seven steps: viral entry, reverse transcription, integration, gene expression, gene assembly, budding, and maturation. HIV reverse transcriptase (RT) is one of the essential enzymes for HIV replication and is therefore one of the major targets in the search for effective therapies.[2] Substantial resources have been allocated for the study of HIV and the development of antiretroviral agents,[3] particularly reverse transcriptase inhibitors (RTIs).[4] RTIs are divided into two categories: nucleoside (NRTIs) and non-nucleoside (NNRTIs) reverse transcriptase inhibitors. NRTIs are phosphorylated by cellular enzymes to an active metabolite, analogous to a natural nucleotide, and then incorporated into the growing viral DNA chain by HIV RT in a competitive reaction. Once inserted into the chain, no further nucleotides can be added, and therefore viral replication ceases. NNRTIs are a diverse group of compounds that inhibit HIV reverse transcription by allosteric binding to the RTs, instead of forming covalent bonds.[5] In contrast to nucleoside analogues, NNRTIs are highly specific for HIV-1 isolates, do not bind to HIV-2 reverse transcriptase, and are effective without toxic side effects at relatively high concentrations.[6] Although combination therapy can slow the emergence of drug-resistant strains of virus, a need exists for the discovery and development of improved NNRTIs. This contribution describes the chemical development of a potent NNRTI, (1*S*,2*S*)-*N*-[*cis*-2-(6-fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-*N*′-[2-(5-cyanopyridyl)]urea, which is also known as MIV-150.[7]

Medicinal Chemistry/Linear Route

The medicinal chemistry route is outlined in Scheme 1. This route was successfully scaled up, with some adjustments, to deliver multiple kilograms of active pharmaceutical ingredient (API) used in toxicology studies and early clinical trials. This route produced material of high purity. However, there were three major concerns. Our first and greatest concern was the asymmetric cyclopropanation step. While practical on smaller scales, scaling-up of this crucial transformation suffers from low yield and poor diastereoselectivity. Although the enantioselectivity of the reaction is usually >98%, the yield is typically 45−55% and the *cis:trans* ratio a disappointing 3:1. Other issues associated with this step include reagent costs and lack of availability as well as safety concerns. The chiral catalyst for the enantioselective cyclopropanation is derived from (D)-*tert*-leucine, which is an expensive unnatural amino acid with few worldwide suppliers who typically quote very long lead times. In addition, ethyl diazoacetate is potentially explosive, making the sourcing and transportation of bulk quantities of this reagent difficult. Our second concern was the low yield (18% for two steps) for the *n*-BuLi-assisted formylation and subsequent Wittig olefination reaction. The last concern was with the linear nature of the route and the associated higher risks for manufacturing. In addition, the linear route has a long lead-time with a low overall yield of 1.0% (5.8% from **1** to **4**, and 18% for the steps from **4** to MIV-150). In anticipation of future deliveries of API, a safe, scalable, efficient and cost-effective synthesis was needed.

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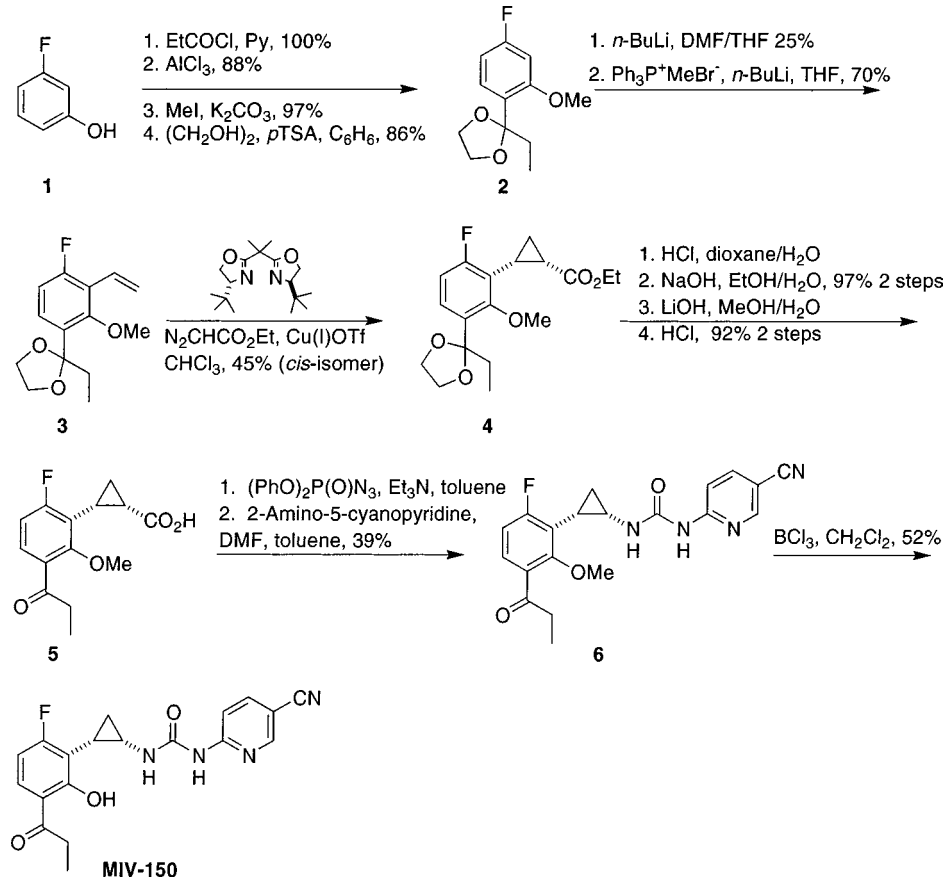
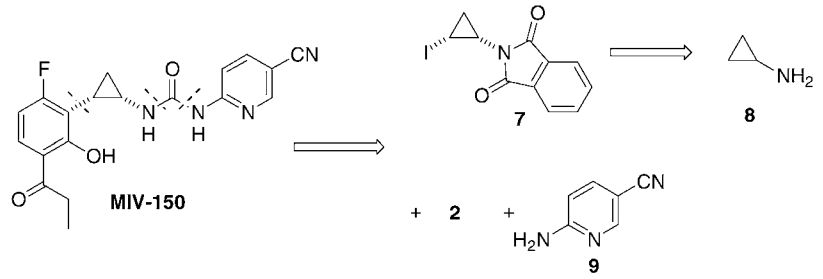
Scheme 1



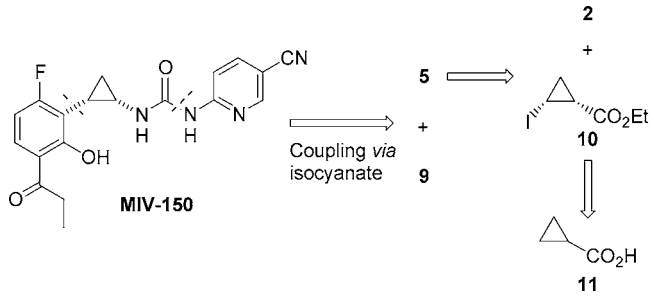
Scheme 2



Original Convergent Route

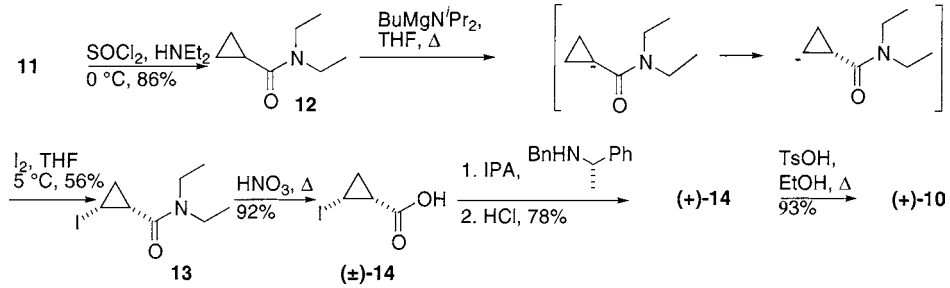
A retro-synthetic analysis of an earlier convergent route is shown in Scheme 2.[8] The key to this convergent strategy would be a metal-mediated cross-coupling reaction between a suitably substituted, enantiopure **7** and fluoroketal **2**. After a great deal of investigation, the medicinal chemistry group at Chiron discovered that a palladium (II)-mediated Negishi reaction could successfully couple fluoroketal **2** to iodocyclopropyl phthalimide (ICP) **7** while maintaining the stereochemical integrity of the cyclopropyl ring. One obvious advantage of this route, besides being convergent, was the ability to capitalize on the known chemistry developed for the synthesis of fluoroketal **2** and to use the same reagent, 2-amino-5-cyanopyridine, **9**, for the asymmetric urea formation step. The synthesis of **7** is a six-step sequence involving the protection of cyclopropylamine with pivaloyl chloride, iodination via a BuLi generated β-dianion, removal of the pivaloyl group, reaction with phthalic anhydride, brucine resolution, and final cyclization. Upon scaling up, however, numerous issues were discovered with the preparation of ICP **7**; the most serious was gel formation during the generation of cyclopropyl pivalamide dianion. The intermediate resulting from the removal of the pivaloyl group possesses a nucleophilic group and an electrophilic center in the same molecule and is intrinsically unstable. Also, the late-stage resolution

Scheme 3



(8) Details of this convergent chemistry will be published in a separate paper.

Scheme 4



calls for the use of brucine, a highly toxic chiral resolving agent, and affords only a moderate yield. Therefore, this convergent route was deemed to be unacceptable for large-scale production.

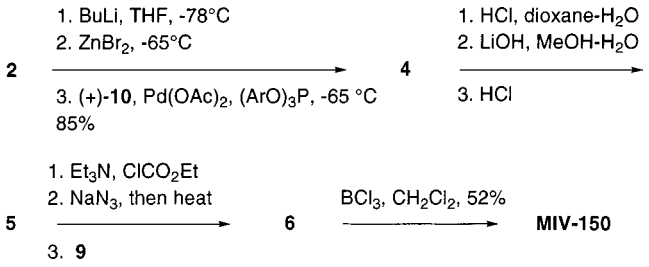
Results and Discussion

Because of the problems with both the linear and the earlier convergent route, we started to look for an alternative synthesis for the production of additional MIV-150. First, we examined and compared the previous two synthetic routes to determine what information was of value. The convergent route was attractive because it demonstrated that the Negishi reaction could reliably and efficiently couple the aryl zinc species derived from **2** to the functionalized iodocyclopropyl ring with retention of configuration. The linear route had demonstrated that it was robust and that the reactions downstream from **5** provided material of high purity. Conceivably, we could take advantage of both routes and assemble the molecule through a similar Negishi coupling of the same aryl zinc species with a functionalized and protected cyclopropanecarboxylic acid moiety (Scheme 3). A logical choice would be *cis*-2-iodocyclopropanecarboxylate, as this would lead to a common late-stage intermediate with the linear route. Preliminary studies indicated that the coupling of **2** with racemic iodoester **10** proceeded well, affording the desired ketoester **4** as a racemate without epimerization at either the α- or the *β*-position of the cyclopropane ring.

It is more desirable to introduce chirality into the molecule at an earlier stage; thus, the focus of the exploration of this new route was shifted to the preparation of enantiomerically pure iodoester **10**. Ideally, the iodo group and chirality would be introduced in a single step into cyclopropanecarboxylic acid **11** or its derivatives. Towards this end, we have attempted several iodination reactions of **11**, its inorganic salts, esters, and secondary amides, with or without a chiral amine in the reaction mixture. The bases used for these reactions included *n*-, *s*-, and *t*-BuLi, Bu_2Mg, and $Mg(N^iPr_2)_2$. Preliminary studies of these reactions proved to be unsuccessful.

Meanwhile, we devised an indirect route to the desired, enantiomerically pure iodoester **10**, by applying the *β*-iodination chemistry discovered by Professor Eaton's group (Scheme 4).[9] Cyclopropanecarboxylic acid **11** was first converted to its tertiary amide **12**. Deprotonation with the mild, chelating base, bis(diisopropylamido)magnesium ($Mg(N^iPr_2)_2$), presumably afforded the α-anion first, which isomerized to afford the *β*-anion with a *cis*-configuration. Iodination with I_2 then gave the desired *β*-iodoamide. $BuMgN^iPr_2$ proved to work more efficiently for this purpose, affording higher yields for the desired *β*-iodination product. The crude reaction mixture from this step, containing the starting material **12** (ca. 6%), the desired product **13** (ca. 83%), and the α-iodination isomer of **12** (ca. 6%), was hydrolyzed in hot 35% nitric acid to afford racemic **14**[10] in 97% purity.

Scheme 5



Racemic acid **14** was resolved with a stable, less toxic, and fairly inexpensive chiral amine, (*S*)-(−)-*N*-benzyl-α-methylbenzylamine, in excellent optical purity and yield (99+% ee and 39% yield for the desired enantiomer). In addition, the chiral amine can be recovered after the acidification of the diastereomeric salt with HCl and subsequently reused for resolution.

The relatively less reactive acid, (+)-**14**, was esterified in quantitative yield by refluxing in ethanol with *p*-toluenesulfonic acid as a catalyst, without loss of enantiomeric purity.

With both the fluoroketal **2** and the enantiomerically pure **10** in hand, the stage was set for the critical Negishi coupling. Under an inert atmosphere and anhydrous conditions using freshly prepared $ZnBr_2$ solution, this reaction went extremely well, affording the desired coupling product **4** in excellent yield. There was no detectable quantity of the *trans*-isomer of **4** in the reaction mixture or isolated product, suggesting that no epimerization at either the α- or *β*-position of the cyclopropyl ring occurred. In the linear route and after the subsequent acidic deketalization step, the *trans* ketone ester was selectively hydrolyzed with NaOH and thus removed from the *cis* ketone ester. Such a step was rendered unnecessary in our new process.

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Table 1. **Aqueous solubilities of MIV-150 salts[a]**

salt form (CAS #)	solubility (mg/mL)	purity (area %)	melting range (°C)	appearance
benzathine (140-28-3)	0.0019	99.0	–	sticky yellow paste
tromethamine (77-86-1)	0.0013	99.8	169.2−169.7	white powder
meglumine (6284-40-8)	0.0017	100.0	162.6−166.2	white powder
diolamine (111-42-2)	0.0013	99.9	154.6−159.2	pale yellow/white powder
olamine (141-43-5)	0.030	97.0	122.3 (dec)	bright yellow powder
ammonium	0.0010	99.9	192.2−194.5	white powder
sodium	0.033	99.6	189.5 (dec)	pale yellow powder
potassium	0.019	99.5	164.3−168.1(dec)	pale brown/white powder
neutral MIV-150	0.000005	100.0	192−194	white powder

[a] NMR analyses conform to the structures of MIV150 and the bases.

The overall process of this hybrid route was successfully completed by carrying intermediate **4** through to MIV-150 (Scheme 5), in a sequence similar to that in the linear route. The reaction mixture from the Negishi coupling step, consisting mainly of **4** and excess **2**, was carried forward through the subsequent acid and basic hydrolysis steps. The neutral impurities (e.g., excess **2**) were removed by extraction before the HCl acidification step. For the urea formation and coupling with 2-amino-5-cyanopyridine, the same acyl azide[11] and isocyanate chemistry was applied. Instead of using expensive reagents, such as diphenyl phosphorazidate, to make the acyl azide precursor, NaN_3[12] was reacted with the mixed anhydride of **5** and $ClCO_2Et$.

To meet and/or surpass the requirements of high purity for the API as set in our specifications, and at the same time streamline the reaction sequence, we have installed a number of check-points at which high purities of the intermediates were required and successfully obtained through distillation, recrystallization, or extraction, while the other steps were telescoped without purification of the crude products. For example, while compound **12** was vacuum distilled, ensuring a highly pure starting material, the following iodination, amide hydrolysis, and chiral resolution steps were telescoped without purification. High chemical and optical purity of the acid **(+)-14** was achieved through crystallization and recrystallization at the optical resolution stage. Similarly, the reaction mixture from the Negishi coupling step containing excess **2** was carried through the subsequent acidic and basic hydrolyses. Neutral impurities were completely removed from the reaction mixture by extraction prior to acidification of the lithium salt of **5**. For the next four steps leading to **6**, no purification was performed on these reactive intermediates. After the BCl_3 demethylation reaction, the crude product was recrystallized in absolute ethanol to afford the final API.

Through this hybrid route, MIV-150 was obtained in good purity and met all of our specification requirements, including those for optical purity and heavy metal residues.

Basic Salts

The aqueous solubility of MIV-150 itself is no more than 5 ng/mL between pH 0.97 and 9.05 and is 12 ng/mL at pH 9.89. These extremely low solubilities pose a great challenge in drug bioavailability and formulation studies. To overcome this limitation, the neutral molecule was converted into various organic and inorganic basic salts via the phenolic hydroxyl functional group by reacting MIV-150 with an equimolar amount of an appropriate base.

Table 2. **Solubilities of MIV-150 salts in buffered aqueous solutions**

sample pH	buffer (0.05 M)	sodium salt (mg/mL)	potassium salt (mg/mL)	olamine salt (mg/mL)
4.01	acetate	0.00078	0.00084	0.00093
5.97	acetate	0.00090	0.00100	0.00120
7.00	phosphate	0.00091	0.00089	0.00108
7.98	phosphate	0.00086	0.00088	0.00103
9.02	carbonate	0.00101	0.00098	0.00111
10.01	carbonate	0.00135	0.00142	0.00154
10.51	carbonate	0.00320	0.00297	0.00289

Saturated solutions of the isolated salts were prepared by equilibrating the salts in deionized water followed by filtration. The solubilities were measured by comparing the peak areas by reversed phase HPLC with those of gravimetrically prepared standards of neutral MIV-150 reference material. The concentration of MIV-150 was calculated for each salt solution. The results of these analyses are tabulated in Table 1 along with the CAS numbers of the organic bases, HPLC purities, melting ranges, and the appearance of the isolated salts. As the data indicate, all of the basic salts have greater aqueous solubility than neutral MIV-150. The increase in solubility ranges from 208 times more soluble for the ammonium salt to 6700 times more soluble for the sodium salt.

Furthermore, we have established the pH-solubility profiles in various buffered solutions for the sodium, potassium, and olamine salts, and the results are tabulated in Table 2. All three salts demonstrated the same trend of increased solubility at elevated pHs.

Conclusions

A significantly improved hybrid formal synthesis of MIV-150 has been developed which incorporates key elements from both the linear and the earlier convergent routes. We were able to capitalize on the proven chemistry of the linear route to prepare our fluoroketal coupling partner **2**. More importantly, the hybrid synthesis merged into the linear route via common late-stage intermediates **4** and **5**, thus allowing

(11) Acyl azides are potentially explosive. Normally their solutions should not be concentrated to dryness.

(12) For safety issues related to the use of sodium azide, refer to Urben, P. G., Ed. *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth-Heinemann: Oxford, UK, 1999; Vol. 1, pp 1802−1804.

the opportunity to use the same final steps and to avoid generating a new/lower impurity profile for the final API. In addition to having lower risks for the manufacturing process, this new hybrid convergent route also affords higher yields with less lead time. The overall yield for preparing the iodoester **(+)-10** was 32%, while the overall yield for the fluoroketal **2** arm was 73%. From the convergent point to the final API, the overall yield was 27%. This is a marked improvement compared to the overall yield of only 1.0% for the linear route. In addition, we have developed procedures to prepare the basic salts with significantly higher solubilities than that for the parent molecule, further facilitating studies in related areas.

Experimental Section

General. Unless otherwise indicated, all anhydrous solvents were commercially obtained and stored in Sure-Seal bottles under nitrogen. All other reagents and solvents were purchased and used without purification. Both (*S*)-(−)-*N*-benzyl-α-methylbenzylamine and (*S*)-(−)-α-methylbenzylamine were purchased from Aldrich. NMR spectra were measured on a Bruker 400 MHz instrument. Chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS at 0.00 or $CHCl_3$ at 7.27 for ^1H, and TMS at 0.00 or $CDCl_3$ at 77.23 for ^{13}C. Coupling constants (J) are reported in hertz. FT-IR spectra were obtained on a Perkin-Elmer Paragon 1000 as KBr pellets or film with a scan range of 4500−500 cm^{-1}. Mass spectra data were acquired on a JEOL LCMate, double-focusing mass spectrometer, in either APCI positive or negative mode. For high-resolution mass spectra, the resolving power was set at 3000. Optical rotations were determined on a Perkin-Elmer model 241 polarimeter. Analytical HPLC was conducted on an Agilent 1100 using a 250 mm × 4.6 mm octadecylsilane (ODS), 5 μm, 100 Å column at a flow rate of 1.0 mL/min, and processed with Chemstation software. Peaks were monitored at 254 or 215 nm. GC analyses were conducted on an Agilent 6890, with either a DB-WAXETR column (30 m × 0.32 mm i.d., and 1 μm film thickness) or a HP-5 column (30 m × 0.32 mm i.d., 0.25 μm film thickness). Peaks were monitored by a flame ionization detector.

Cyclopropyl-*N*,*N*-diethylcarboxamide (12). A 2-L, three-necked reactor equipped with an overhead stirrer, thermometer, a pressure equalizing addition funnel, and a heating mantle was charged with thionyl chloride (430 mL, 5.89 mol, 1.01 equiv). Cyclopropanecarboxylic acid (500.0 g, 5.80 mol) was then added via the addition funnel to the stirred thionyl chloride. The reaction was endothermic, and heat was applied during the addition to maintain a temperature between 0 and 5 °C. After the addition was completed, stirring was maintained at 20 °C, and the reaction progress was monitored by GC. An additional 5-L, three-necked flask equipped with an overhead stirrer, thermometer, a pressure-equalizing addition funnel, and an ice bath was charged with diethylamine (1.26 L, 12.1 mol, 2.08 equiv) and dichloromethane (DCM) (2 L) and cooled to 0 °C. The acid chloride solution was transferred to the addition funnel and added to the cooled diethylamine solution at such a rate that the temperature could be maintained between 25 and 30 °C. After the addition, the reaction mixture was stirred at 25 °C and monitored by GC for completeness. When the reaction was complete, water (1 L) was added. The phases were separated, and the opaque yellow organic layer was washed with 2 M HCl (500 mL), 20% aqueous solution of $NaHCO_3$, and NaCl (25% aqueous solution, 600 mL). Solvent was removed under reduced pressure and the product isolated by simple vacuum distillation (bp: 97−100 °C, 20 mmHg) as a clear, colorless liquid (706 g, 86%). HPLC purity: 100%. ^1H NMR ($CDCl_3$) δ 3.49 (q, 2H, J = 7), 3.39 (q, 2H, J = 7), 1.69 (m, 1H), 1.25 (t, 3H, J = 7), 1.11 (t, 3H, J = 7), 0.97 (m, 2H), 0.74 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 172.92, 42.46, 41.23, 15.15, 13.63, 11.52, 7.77. FT-IR (neat, cm^{-1}): 3009, 2975, 2934, 1640, 1259, 1139. HRMS (*m*/*z*) for $C_8H_{16}NO$ ($M^+ + 1$): calcd 142.1232, found 142.1192.

(±)-(*cis*)-2-Iodocyclopropyl-*N*,*N*-diethylcarboxamide (±)-13. A 3-L, four-necked reactor equipped with an overhead stirrer, thermometer, and pressure equalizing addition funnel was charged with dibutylmagnesium (1.0 M in heptane, 372 mL, 372 mmol). Diisopropylamine (52.0 mL, 372 mmol) was added via an addition funnel, keeping the internal temperature below 40 °C. The reaction mixture was allowed to stir without external heating for 45 min and then heated to reflux for 5 min and allowed to cool to room temperature. A solution of **12** (50.0 g, 355 mmol) in anhydrous THF (600 mL) was added via addition funnel. Heating was resumed and the reaction mixture was refluxed for 1 h. To a separate 5-L reactor equipped with an overhead stirrer and thermometer was added iodine (180.0 g, 709 mmol) and anhydrous THF (900 mL). The mixture was stirred at room temperature[13] until all iodine had dissolved, and then the solution was cooled to −20 °C. Heating of the diethylamide anion was discontinued and the solution cooled to 5 °C before being added via cannula to the reactor containing I_2/THF. The reaction was slightly exothermic, and the rate of addition was controlled so as to keep the internal temperature below 0 °C. After complete addition, the reaction mixture was stirred at 0 °C for 15 min and then transferred to a separatory funnel containing 150 mL of concentrated H_2SO_4. The THF phase was concentrated under vacuum and the resulting aqueous solution was extracted with DCM (2 × 500 mL). The combined organic phases were washed with 12% aqueous solution of $Na_2S_2O_3$ (3 × 300 mL) and brine (1 × 300 mL). The combined extracts were concentrated under reduced pressure to give a dark oil (79.6 g of crude product, 66% w/w for the desired product, yield: 56%). For a sample purified by column chromatography, ^1H NMR ($CDCl_3$): δ 3.62 (m, 2H), 3.37 (dt, 1H, J_1 = 14.9, J_2 = 7.2), 3.24 (dt, 1H, J_1 = 13.6, J_2 = 7.1), 2.81 (dt, 1H, J_1 = 5.8, J_2 = 8.1), 1.94 (dt, 1H, J_1 = 6.3, J_2 = 8.4), 1.58 (q, 1H, J = 6.0), 1.41 (dt, 1H, J_1 = 6.2, J_2 = 8.0), 1.26 (t, 3H, J = 7.2), 1.17 (t, 3H, J = 7.1). ^{13}C NMR ($CDCl_3$): δ 168.06, 42.10, 41.16, 19.44, 14.72, 14.65, 13.73, −13.27. FT-IR (neat, cm^{-1}): 2974, 2933, 1640, 1262, 1236, 1140. HRMS (*m*/*z*) for $C_8H_{15}INO$ ($M^+ + 1$): calcd 268.0199, found 268.0253.

(13) Heating a solution of iodine in THF may cause a free radical decomposition of the solvent.

(±)-(*cis*)-2-Iodocyclopropanecarboxylic Acid (±)-14. A 1-L, three-necked flask was equipped with an overhead stirrer, thermometer, and a reflux condenser. Compound **13** (66.5 g, 0.249 mol) was charged to the flask. An aqueous solution of HNO_3 (170 mL of 63% HNO_3 and 160 mL of water) was added. The reaction mixture was stirred and heated to reflux for 20 h, and a second portion of concentrated HNO_3 (68 mL, 63%) was added. Reaction progress was monitored by HPLC. Upon reaction completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 200 mL). The combined ethyl acetate extracts were washed with brine (2 × 300 mL), dried over $MgSO_4$, filtered, and concentrated to give a light yellow solid (48.6 g, 92%). HPLC purity: 97%. ^{1}H NMR ($CDCl_3$): δ 2.89 (m, 1H), 1.95 (m, 1H), 1.55 (m, 1H), 1.42 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 176.29, 19.37, 17.66. FT-IR (KBr, cm^{-1}): 3040 (br), 1699, 1224. HRMS (*m*/*z*) for $C_4H_4IO_2$ ($M^- - 1$): calcd 210.9256, found 210.9292.

(1*R*,2*R*)-2-Iodocyclopropanecarboxylic Acid (+)-14. To a jacketed, 4-L cylindrical reaction vessel that was equipped with a circulating heating/cooling bath, a water condenser, a N_2 inlet, an overhead stirrer, and an internal temperature probe was charged a solution of the racemic acid **14** (311.1 g, 1.47 mol) in 2170 mL of 2-propanol and a solution of (*S*)-(−)-*N*-benzyl-α-methylbenzylamine (311.1 g, 1.47 mol, 1.00 equiv) in 1240 mL of 2-propanol. A suspension of the salt began to form within 5 min and was heated to 75 °C. The suspension turned clear and was then cooled. The onset of crystallization occurred at around 56 °C. The slurry was held at 53 °C, stirred for 30 min, and cooled further to 20 °C. The crystalline solid was collected by vacuum filtration, washed with 2-propanol (2 × 670 mL), and air-dried (260.0 g). The partially resolved salt was mixed with 1910 mL of 2-propanol, and the mixture was heated to 76 °C and cooled. The crystalline salt was collected by vacuum filtration, washed with 2-propanol (2 × 350 mL), and dried to give the product (243.3 g, 39% yield). HPLC purity: 99.8%.

To a 4-L reactor were added the above salt (241.3 g, 0.57 mol), 1340 mL of 0.5 N NaOH (0.67 mol, 1.2 equiv) and 670 mL of DCM. The mixture was stirred for 5 min and transferred to a 4-L separatory funnel. After draining off the DCM layer, the aqueous layer was washed with DCM (2 × 670 mL) and acidified with 2 M HCl (670 mL). The resolved iodoacid was extracted with *tert*-butyl methyl ether (TBME, 3 × 670 mL). The combined TBME extracts were washed with brine, dried over $MgSO_4$, filtered, concentrated on a rotavap and further concentrated at 0.5 Torr at room temperature for 30 min. The product solidified as a white solid (117.9 g, 98% yield). Mp = 68.8−70.1 °C. HPLC purity: 98.2%. Enantiomeric excess by GC: 99.1% (vide infra). $[\alpha]^{24}_D$ = +47.22 (*c* 0.10, MeOH). ^{1}H NMR ($CDCl_3$): δ 2.91 (dt, 1H, J = 6.7, 8.2), 1.92 (dt, 1H, J = 6.4, 8.3), 1.60 (dt, 1H, J = 6.2, 8.2), 1.44 (q, 1H, J = 5.4). ^{13}C NMR ($CDCl_3$): δ 176.71, 19.80, 17.71, −14.29. FT-IR (KBr, cm^{-1}): 3091 (br), 1707, 1223. HRMS (*m*/*z*) for $C_4H_4IO_2$ ($M^- - 1$): calcd 210.9256, found 210.9261.

Determination of Enantiomeric Excess (ee) of the Resolved Acid (+)-14. To a 10-mL round-bottomed flask were charged 200 mg (0.94 mmol) of the resolved *cis*-2-iodocyclopropanecarboxylic acid and 1 mL of DCM. Under an N_2 atmosphere, $SOCl_2$ (0.14 mL, 1.86 mmol, 2.0 equiv) was added. The reaction mixture was stirred at room temperature for 45 min. (*S*)-(−)-α-Methylbenzylamine (0.48 mL, 3.76 mmol, 4.0 equiv) in 3 mL of DCM was added to the acid chloride solution which was cooled in an ice bath. The resulting reaction mixture was stirred at room temperature for 1 h. Some precipitates formed which did not interfere with the de determination. An aliquot (0.1 mL) of the suspension was diluted with MeOH (ca. 1.5 mL). The resulting clear solution was diluted 3× with MeOH and analyzed by GC. The diastereomeric excess of the diastereomeric amides represents the enantiomeric excess of **14**.

Ethyl (1*R*,2*R*)-2-Iodocyclopropanecarboxylate (+)-10. A 2-L, four-necked reactor equipped with an overhead stirrer, thermometer, and reflux condenser was charged with the resolved iodoacid **(+)-14** (114.0 g, 538 mmol), *p*-toluenesulfonic acid, (5.10 g, 26.8 mmol, 0.05 equiv), and absolute ethanol (1.14 L). The reaction mixture was stirred and heated to reflux for 24 h. Reaction completion was monitored by HPLC. The reaction mixture was allowed to cool to room temperature and the solvent removed under reduced pressure. The resulting liquid residue was taken up in EtOAc (1.6 L) and water (60 mL), washed with saturated $NaHCO_3$ (2 × 170 mL) and brine (1 × 170 mL), dried over $MgSO_4$, filtered, and concentrated to give a colorless oil (120.0 g, 93% yield). Purity: 99.2% by GC and 98.2% by HPLC. Bp = 38.5 °C/260 mTorr. $[\alpha]^{24}_D$ = +32.54 (*c* 0.10, MeOH). ^{1}H NMR ($CDCl_3$): δ 4.23 (m, 2H), 2.81 (dt, 1H, J = 6.5, 8.1), 1.87 (dt, 1H, J = 6.4, 8.3), 1.52 (dt, 1H, J = 6.2, 8.2), 1.41 (q, 1H, J = 5.4), 1.31 (t, 3H, J = 7.1). ^{13}C NMR ($CDCl_3$): δ 170.14, 61.47, 19.46, 16.55, 14.66, −14.36. FT-IR (neat, cm^{-1}): 3060, 2982, 2937, 1728, 1279, 1249, 1178. HRMS (*m*/*z*) for $C_6H_{10}IO_2$ ($M^+ + 1$): calcd 240.9726, found 240.9696.

Ethyl (1*S*,2*S*)-2-[3-(2-Ethyl(1,3-dioxolan-2-yl))-6-fluoro-2-methoxyphenyl]cyclopropanecarboxylate (4). A 3-L, five-necked round-bottomed flask equipped with an overhead mechanical stirrer, temperature probe, pressure equalizing addition funnel, and a N_2 inlet was charged with 1-(2-ethyl-(1,3-dioxolan-2-yl))-4-fluoro-2-methoxybenzene **2** (131.2 g, 580 mmol) and THF (850 mL) at room temperature. The stirred solution was then cooled to −78 °C. *n*-Butyllithium (213.8 mL, 2.5 M in hexanes, 555.8 mmol) was added dropwise via the addition funnel at a rate so that the internal temperature did not rise above −70 °C. The solution gradually became yellow and remained homogeneous. After the addition of *n*-BuLi was complete, the mixture was stirred at −70 °C for 3 h during which time white precipitates formed on the inside wall of the flask. During the 3 h stir period, a fresh 1.6 M solution of zinc bromide in THF was prepared: a 1-L, three-necked flask under N_2 with magnetic stirring was charged with THF (350 mL) and cooled to 0 °C. Nitrogen was rapidly flushed through the system, and zinc bromide (125.2 g, 555.9 mmol) was added in portions to the stirred solution. The zinc bromide solution was allowed to warm to room temperature and then transferred to an

addition funnel. Addition of the zinc bromide THF solution to the aryllithium solution commenced after the 3 h stir period expired, at a rate that maintained the internal temperature below −65 °C. After the addition was complete, the pale yellow homogeneous arylzinc solution was allowed to warm to room temperature. A solution of ethyl (1*S*,2*S*)-2-iodocyclopropylcarboxylate **10** (116.0 g, 483.3 mmol), palladium acetate (1.09 g, 4.83 mmol), and tris(2,4-di-*tert*-butylphenyl) phosphite (15.63 g, 24.2 mmol) in THF (225 mL) was prepared. The resultant clear, orange solution was stirred for 10 min, transferred to an addition funnel and added to the arylzinc solution. The resultant reaction mixture was heated to reflux (∼64 °C). The reaction was deemed complete when GC analysis indicated that less than 2% iodide was present, typically within 24 h. The solvent was removed under reduced pressure and replaced with ethyl acetate (1.5 L). To this solution was added 2 M NaOH (1.0 L), which resulted in gel-like white precipitates. The slurry was filtered through Celite, and the filter cake was rinsed with EtOAc (200 mL) and water (200 mL). The organic layer of the filtrate was separated and the aqueous phase extracted with EtOAc (2 × 100 mL). The organic extracts were combined, washed with 2 M NaOH (2 × 500 mL), water (200 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to give 168 g of **4** as an oil that slowly crystallized (170 g, 85% yield, 84.8% purity by HPLC (the residual being **2**)). The following analytical data are from a purified sample obtained through column chromatography. Mp = 71.0−72.0 °C. $[\alpha]^{24}_D$ = +368 (*c* 2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.32 (m, 1H), 6.74 (t, 1H, *J* = 8.0), 4.03−3.80 (m, 9 H), 2.21−2.04 (m, 4H), 1.60 (m, 1H), 1.53 (m, 1H), 1.08 (t, 3H, *J* = 7.1), 0.79 (t, 3H, *J* = 7.4). ^{13}C NMR ($CDCl_3$): δ 171.68, 164.33, 161.87, 159.22, 130.25, 126.80, 119.0, 110.74, 109.86, 109.64, 64.72, 61.31, 60.09, 31.35, 20.08, 15.72, 14.01, 8.10. MS: 339.2 ($M + H^+$). FT-IR (KBr, cm^{-1}): 2981, 2944, 2887, 1722, 1603, 1198, 1172, 1054. HRMS (*m*/*z*) for $C_{18}H_{24}FO_5$ ($M^+ + 1$): calcd 339.1608, found 339.1600.

General Procedure for the Preparation of Basic Salts. Neutral MIV-150 was dissolved in DCM at a concentration of 1 g per 100 mL, and an equimolar amount of base was added. In cases where base was not soluble in DCM, the base was first dissolved in 1 mL of water which was then added to the solution. The solutions were stirred for 30 min, and the solution was concentrated at reduced pressure to leave solid material, except in the case of the benzathine salt which formed a yellow paste. The benzathine salt paste was dried at high vacuum until a constant weight was obtained.

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