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Design of Concise, Scalable Route to a Cholecystokinin 1 (CCK 1) Receptor Antagonist

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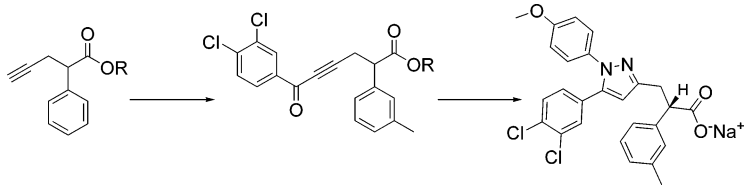

Development of efficient, scalable routes for the synthesis of (*S*)-3-[5-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-*m*-tolyl propionic acid, a selective cholecystokinin 1 (CCK 1) receptor antagonist, is described. A key feature of the scale-up route is a concise construction of the complete pyrazole framework in a single step by reacting an aryl hydrazine with an elaborated acetylenic ketone. This route was then further refined incorporating efficient enantioselective strategies to obtain the desired *S*-enantiomer in high optical purity. The first strategy involved an efficient, recyclable, kinetic resolution by enzyme-catalyzed hydrolysis of the racemic ester. In the second-generation route, the requisite stereochemistry at the chiral center was generated at an early stage in the synthesis involving a remarkable diastereoselective addition of inexpensive (*S*)-(−)-ethyl lactate to an alkylaryl ketene. Both methods furnished optically pure (>99% ee) final drug substance as its crystalline sodium salt.

Introduction

Cholecystokinin (CCK) is a polypeptide hormone (33 amino acids) located both in the gastrointestinal system and in the central nervous system.[1] Triggered by ingestion of food, the release of CCK hormone is the primary event that leads to the myriad of physiological effects in the GI tract. CCK appears to stimulate basal acid secretion, regulate GI motility, inhibit gastrin-stimulated acid secretion, regulate gall bladder emptying, stimulate the endocrine and exocrine functions of the pancreas, and mediate hunger after meal. These effects of the CCK hormone are initiated by binding to two G-protein-coupled receptors: CCK 1 and CCK 2. Some of the important physiological events, such as stimulation of gall bladder contraction, pancreatic enzyme secretion, duodenal motility, and gastric secretion, have been attributed specifically to the agonism of the CCK 1 receptor by the hormone. Development of selective, small molecule *antagonists* of CCK 1 receptors therefore offers considerable potential in the treatment of GI or pancreatic disorders such as GI motility diseases, dyspepsia, and irritable bowel syndrome (IBS).[2]

Recent efforts from our "Hit-to-Lead" group have led to the discovery of a novel class of pyrazole compounds showing potent CCK 1 antagonist activity and efficacy in animal models for early stage pancreatitis.[3] Among these, compound **1** was identified as a promising candidate for further profiling due to its excellent CCK 1/CCK 2 selectivity, pharmacokinetics, and a number of other desirable pharmacological properties. A practical synthesis suited for large-scale preparation was therefore needed. We wish to report herein the development of a concise and scalable synthetic route to this promising candidate. Our investigations demonstrate the advantages of acetylenic ketones as a more desirable substrate for the synthesis of complex pyrazole structures compared to the traditionally

(1) (a) Ivy, A. C.; Oldberg, E. *Am. J. Physiol*. **1928**, *86*, 599−613. (b) Mutt, V.; Jorpes, E. *Biochem. J*. **1971**, *125*, 57−58.

(2) de Tullio, P.; Delarge, J; Pirotte, B. *Exp. Opin. Invest. Drugs* **2000**, *9*, pp 129−146; Patent WO 2004/007463 A1.

(3) (a) McClure, K.; Hack, M.; Huang, L.; Sehon, C.; Morton, M.; Li, L.; Barrett, T. D.; Shankley, N.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 72−76. (b) Sehon, C.; McClure, K.; Hack, M.; Morton, M.; Li, L.; Barrett, T. D.; Shankley, N.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 77−80.

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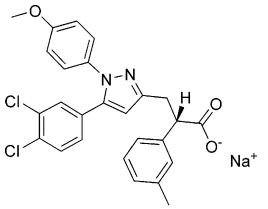
used 1,3-dicarbonyl substrates. Two stereoselective strategies, one, a kinetic resolution using enzymatic ester hydrolysis, and the second, involving a versatile 1,4-asymmetric induction protocol were developed as efficient methods to prepare the drug substance in high (>99%) enantiopurity.



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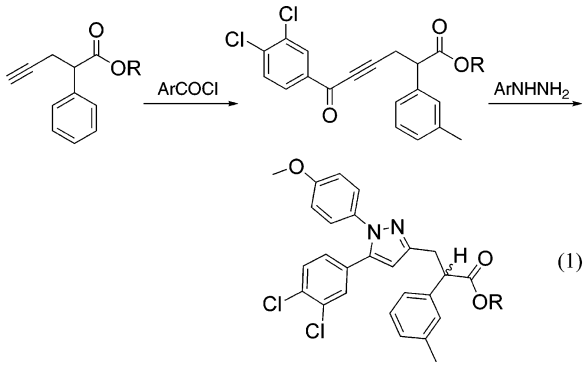
Results and Discussions

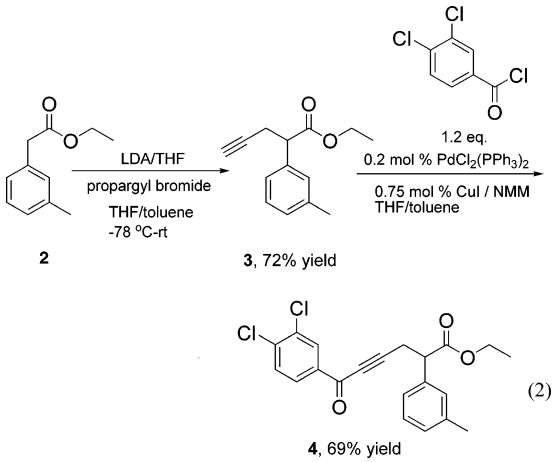
Optically active compound **1** was originally prepared in milligram quantities by a racemic synthesis[3a] followed by chiral chromatographic separation of enantiomers utilizing a preparatory SFC Chiralpak AD column with 40% IPA as eluent. The (*S*)-acid was converted to its sodium salt to obtain the drug substance. In our initial large-scale preparation of the drug substance, we employed an asymmetric variant of this route[4] based on Evans's enantioselective enolate-alkylation strategy.[5] Though this route was optimized to provide us multigram quantities of **1** and satisfied our initial requirements, the lengthy route involving multiple functional group manipulations, column chromatographic purifications, and, in particular, use of an expensive chiral auxiliary prompted us to explore other approaches to this molecule that are more practical for large-scale synthesis.

The Knorr pyrazole synthesis[6] involving the condensation of a hydrazine with a 1,3-dicarbonyl substrate is perhaps the most widely used method for the construction of simple pyrazole structures. However, in the case of complex molecules with a pyrazole core, construction of highly elaborated, unsymmetrical 1,3-dicarbonyl substrates is not always very practical. Initial construction of the basic pyrazole core and subsequent elaboration as exemplified in our earlier syntheses[3a,4] is thus the strategy most often adopted. In this context, pyrazole synthesis by the condensation of acetylenic ketones with hydrazines[7] offers some distinct advantages. First, alkynones with substituents carrying sensitive functionalities can now be readily constructed by a variety of acetylenic coupling reactions[8] under very mild conditions, offering substantial advantage in step economy; second, the differentiated electrophilic centers of acetylenic ketones offer potential for a better control of regioselectivity.[9] The more electrophilic acetylenic carbon can be expected to react preferentially with the more nucleophilic nitrogen of the hydrazine and thus should afford preferentially the 1,5-regioisomer in the case of aromatic hydrazines.[10] Our approach for **1** is outlined in eq 1.



(1)

The desired acetylenic ketone **4** can be prepared very efficiently from inexpensive reagents in two steps as outlined in eq 2. The lithium enolate of ethyl *m*-tolyl acetate was treated



(2)

with propargyl bromide in THF to give the propargyl ester **3** in 72% yield after fractional distillation. Palladium-catalyzed Sonogashira coupling of **3** with 3,4-dichlorobenzoyl chloride proved more problematic than we anticipated. Thus, the standard protocol (using $PdCl_2(PPh_3)_2$ and CuI as catalysts and triethyl amine in THF at room temperature) gave poor yield (ca. 30%) of the desired acetylenic ketone **4**. Formation of a number of intractable side products was observed, and proton NMR of the crude product showed vinylic protons suggesting isomerization of the acetylene to the corresponding diene and its further decomposition. Isomerization of alkynes to thermodynamically more stable conjugated dienes is a rarely observed occurrence due to the kinetic barrier for the prototropic shift of a methylene proton from the allene intermediate.[11] However, the situation

(4) See Supporting Information for details of this route.

(5) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737−1739. (b) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 1−110. (c) Ghosh, A. K.; Duong, T. T.; McKee, S. P. *J. Chem. Soc., Chem. Commun*. **1992**, 1673−1674. (d) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc*. **1990**, *112*, 4011−4030. (e) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett*. **1987**, *28*, 6141−6144.

(6) (a) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem*. **1966**, *6*, 347−429. (b) Elguero, J. Pyrazoles. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 5, pp 167−303. (c) Elguero, J. Pyrazoles. In *Comprehensive Heterocyclic Chemistry*; Shinkai, I., Ed.; Pergamon: Oxford, 1996; Vol. 3, pp 1−75. (d) Murray, W.; Wachter, M. *J. Heterocycl. Chem*. **1989**, *26*, 1389−1392.

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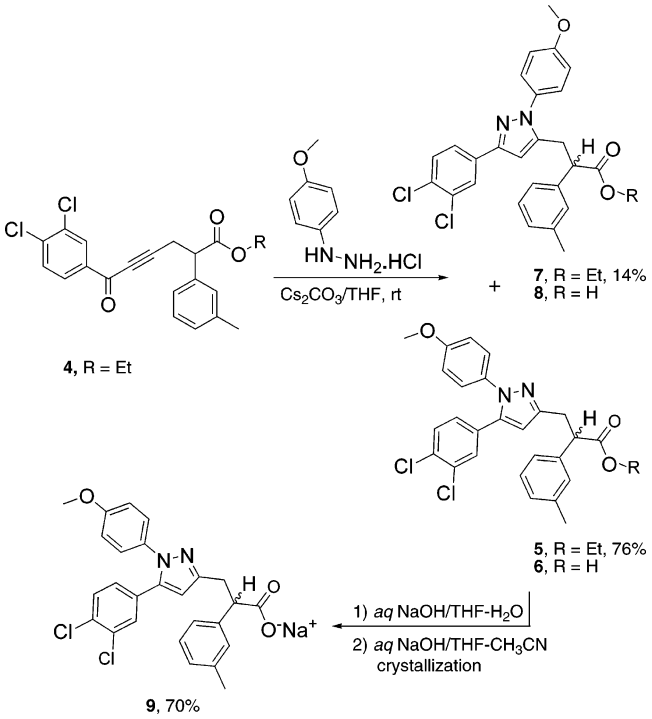
(8) (a) Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011−7016. (b) Grotjahn, D. B.; Van, S.; Combs, D.; Lev, D. A.; Schneider, C.; Rideout, M.; Meyer, C.; Hernandez, G.; Mejorado, L. *J. Org. Chem*. **2002**, *67*, 9200−9209.

(9) (a) Cabarrocas, G.; Ventura, M.; Maestro, M.; Mahia, J.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2483−2493. (b) Miller, R. D.; Reiser, O. *J. Heterocycl. Chem*. **1993**, *30*, 755−763.

(10) Bishop, B. C.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. *Synthesis* **2004**, *1*, 43−52.

(11) (a) *Acetylenic Compounds in Organic Synthesis*; Accademic Press: New York, 1995. (b) *The Chemistry of Carbon-Carbon Triple Bond*, Part 1; John Wiley and Sons: New York, 1978; Chapter 10, pp 381−445.

SCHEME 1



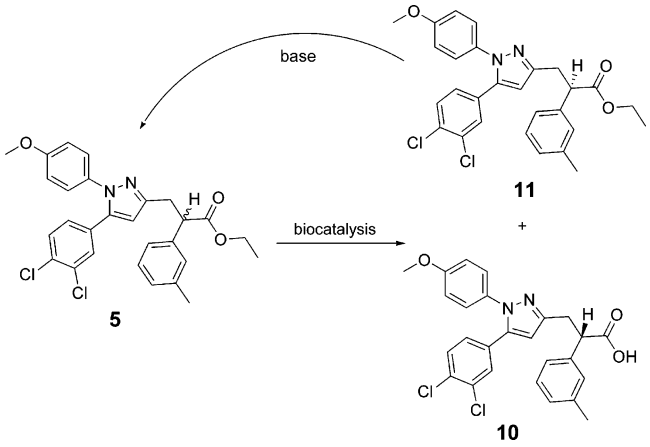
is considerably different in systems with activated methylene groups such as 4-pentynoic acid derivatives, and a proclivity for this base-catalyzed prototropic shift has been noted.[12] We reasoned that use of a milder base could potentially alleviate this difficulty. A number of organic bases were thus screened, and *N*-methylmorpholine was found to be the most suitable to avoid the isomerization. A 1:1 mixture of THF/toluene was found to be the most preferred solvent system, furnishing the acetylenic ketone **4** as pale yellow oil in 69% isolated yield.

We also found that the acetylenic ketone **4** is very sensitive to aqueous acidic media and that care should be taken to avoid strongly acidic conditions during workup. Thus, a solution of **4** in ethyl acetate when exposed to aqueous 1 N HCl was found to hydrate cleanly to form the corresponding 1,3-diketone.

Condensation of acetylenic ketone **4** with 4-methoxyphenylhydrazine, as expected, resulted in the formation of the desired pyrazole **5** as the major regioisomer. However, a significant amount of the undesired 1,3-regioisomer was also formed (see Scheme 1). Our attempts at improving the regioselectivity revealed some intriguing solvent dependency on the regiochemistry. For example, at room temperature, in polar, aprotic solvents such as THF and DMF, the desired 1,5-regioisomer **5** was obtained as the major product along with 15−20% of the undesired 1,3-regioisomer **7**. In protic solvents such as MeOH, EtOH, and IPA, however, the undesired **7** was the major product along with a small amount of the desired isomer **5**. All our attempts to obtain exclusively the desired 1,5-regioisomer were thus unsuccessful. The crude pyrazole product was isolated as an oil, and our attempts at purification by crystallization were also equally unsuccessful. The isomeric mixture was therefore purified by silica gel column chromatography. Although the undesired regioisomer could be easily separated by chromatography, this raised a concern for large-scale synthesis.

(12) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc*. **1988**, *110*, 2301−2303 and references cited therein.

SCHEME 2



A practical solution to the problem was achieved by developing an efficient crystallization of the sodium salt. Thus, alkaline hydrolysis of the crude mixture of the pyrazole esters furnished the corresponding regioisomeric mixture of acids (**6** + **8**). Salt formation by treatment with concentrated aqueous NaOH in THF followed by crystallization from a 1:1 mixture of THF/acetonitrile, we were pleased to find, crystallized the 1,5-regioisomer **9**, completely rejecting the 1,3-regioisomer in excellent recovery. Thus, using the acetylenic route, we avoided the functional group manipulations involved in the dicarbonyl-based route and were able to prepare the racemic drug substance **9** in five steps very efficiently starting from readily available starting materials.

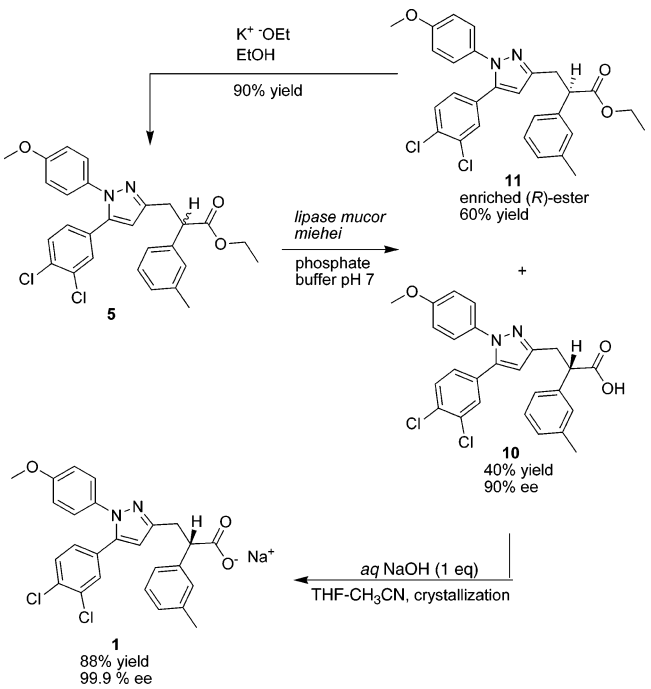
With a concise route to the racemic form of the drug substance now in hand, we next focused our attention on how to use this approach to prepare the drug substance in enantiopure form.

Hydrolytic enzymes such as esterases and lipases have been used for the kinetic resolution of racemic acids by ester hydrolysis on industrial scale.[13] High selectivity, mild reaction conditions, and environmentally sound technology makes biocatalysis an attractive option for large-scale synthesis. The most advantageous scenario for us would be to find an enzyme that selectively hydrolyzes the (*S*)-aryl propionate ester to the (*S*)-aryl propionic acid **10**. This would allow further improvement to the process by recycling the unhydrolyzed (*R*)-aryl propionate ester **11** by a base-catalyzed racemization process (as outlined in Scheme 2).

A variety of commercially available hydrolytic enzymes were screened for stereoselective hydrolysis. Typically, an enzymatic hydrolysis screen was carried out in an aqueous phosphate buffer containing enzyme catalyst (50 mg) with the substrate ester (25 mg) dissolved in a minimum amount of an organic solvent (isopropanol or toluene) and an incubation time of 24−48 h. Of the 54 enzymes[14] tested, only two enzymes provided noteworthy selectivity for the (*S*)-ester. We found the enzymes *lipase mucor miehei* and the Altus #8 (obtained from Altus Biologics) similarly catalyzed hydrolysis of our substrate with

(13) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem*. **2006**, *4*, 2337−2347. (b) Armstrong, J. D., III; Martinelli, M. J.; Senanayake, C. S. *Tetrahedron: Asymmetry* **2003**, *14*, 3425−3426. (c) Kataoka, M.; Shimizu, K.; Sakamoto, K; Yamada, H.; Shimizu, S. *Appl. Microbiol. Biotechnol.* **1995**, *43*, 974−977. (d) Shimizu, S.; Kataoka, M.; Shimizu, K; Hirakata, M.; Sakamoto, K.; Yamada, H. *Eur. J. Biochem*. **1992**, *209*, 383−390. (e) Shimizu, S.; Kataoka, M. *Ann. N.Y. Acad. Sci*. **1996**, *799*, 650−659.

SCHEME 3

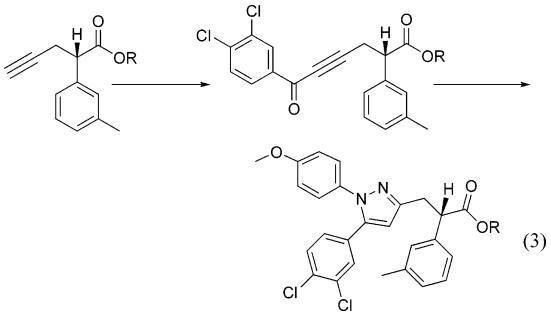


a high degree of enantioselectivity. With the screen results in hand, we proceeded to scale up the enzymatic hydrolysis (as outlined in Scheme 3). The racemic ester dissolved in a minimum amount of IPA (12% by weight) to form a clear solution was added to a solution containing *lipase mucor miehei* in aqueous phosphate buffer at pH 7. Monitoring the reaction by chiral HPLC analysis showed a very selective but slow hydrolysis. After stirring for 10 days at room temperature, when 80% of the (*S*)-ester was consumed, the reaction was arrested. Extractive workup and chromatographic purification afforded the enriched (*S*)-aryl propionic acid **10** in 40% yield with a high degree of enantioselectivity (>90% ee). Higher enantioselectivity of >99% ee was further achieved by salt formation and recrystallization to obtain the (*S*)-sodium carboxylate salt **1** in 88% yield. The enriched (*R*)-aryl propionate ester **11** was easily recycled to racemic **5** in 90% yield upon treatment with potassium ethoxide in ethanol at room temperature. Interestingly, other alkoxide bases such as lithium and sodium ethoxide in ethanol failed to racemize the ester efficiently at room temperature.

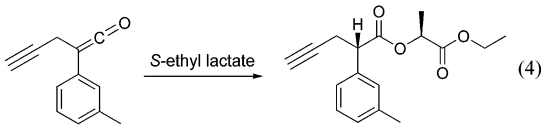
Synthesis of **1** thus was achieved in five steps with an overall yield of 13%. In a 10 g batch, one racemization and recycling step increased the overall yield to about 20%.

While the kinetic resolution proved to be very practical on multigram scale, high cost of the enzyme catalyst, long reaction time, the need for chromatographic purification of **5**, and the need to recycle to improve efficiency were of some concern to us. Although these issues could be overcome by further refinement, we reasoned that perhaps by introducing the chiral center at an early stage through a more cost-effective chiral technology should make the synthesis more efficient.

(14) Two screening test kits were purchased. Screening kit ChiroScreen-EH containing 30 enzymes was purchased from Altus Biologics Inc., 625 Putnam Ave., Cambridge, MA 02139−4211. Web site: www.Altus.com. Tel: 1-888-258-2532. Fax: 1-617-299-2999. Screening set CHIRAZYME Lipases & Esterases containing 24 enzymes were purchased from BioCatalytics, 129 Hill Ave., Suite 103, Pasadena, CA 91106−1955. Tel: (626) 585-9797. Fax: (626) 356-3999. Both enzyme sets are suited for hydrolysis and transesterification reactions.

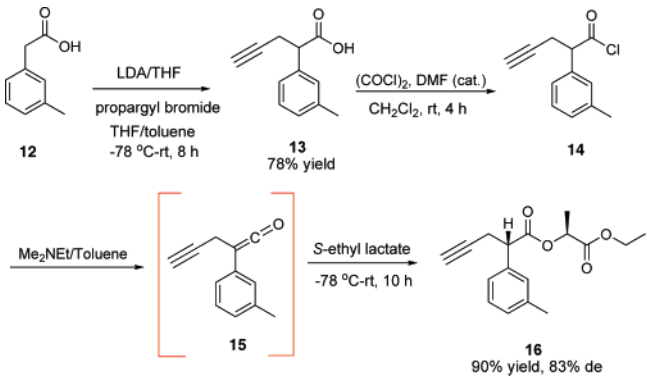


Looking at the synthesis of the acetylenic ketone, it appeared to us that the arylpentynoic acid should be a good point to introduce chirality (see eq 3). A number of methods based on the extensive work reported on the synthesis of nonsteroidal anti-inflammatory (NSAI) agents with 2-arylpropionic acid pharmacophore[15] appeared suitable to access this chiral center. Among these, we were particularly attracted to the possibility of taking advantage of a remarkable 1,4-asymmetric induction observed during the addition of chiral alcohols to ketenes.[16] Merck scientists have further developed this reaction and have shown that, in the case of alkylaryl ketenes, the addition of α-hydroxyesters and lactones proceeds with impressive diastereoselectivity.[17] They have also shown that addition of (*S*)-hydroxy acid such as (*S*)-ethyl lactate to an arylketene predictably introduced *S*-configuration in the newly formed chiral center. The desired (*S*)-arylpentynoic acid derivative could thus be derived from inexpensive, natural (*S*)-ethyl lactate as outlined in eq 4.



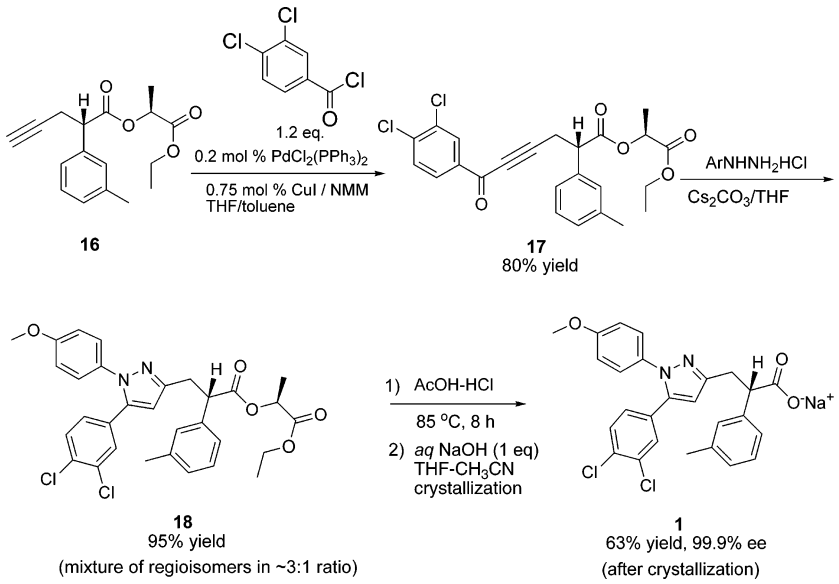
Racemic pentynoic acid **13** was prepared by the alkylation of *m*-tolyl acetic acid with propargyl bromide in excellent yields (Scheme 4). The acid chloride **14** was prepared by treatment

SCHEME 4



with oxalyl chloride. Following the reported procedure, the acid chloride was then reacted with dimethylethyl amine in toluene at 0 °C to generate the ketene **15**. Quenching the reaction with neat (*S*)-ethyl lactate at −78 °C furnished the lactate ester **16** in 90% yield with 83% de. Since the lactate ester could result from both ketene as well as the racemic acid chloride, it is important to ensure complete transformation of acid chloride to ketene for high diastereoselectivity. Using ReactIR in-process

SCHEME 5



monitoring,[18] we found that the ketene formation is quite rapid and was complete in about 5 min at 0 °C.

Sonogashira coupling of the lactate ester **16** with the 3,4-dichlorobenzoyl chloride using our modified procedure furnished the acetylenic ketone **17** in 80% yield (Scheme 5). Proton NMR showed no appreciable changes in diastereomeric ratio (~9/1), indicating that no racemization of the newly formed chiral center took place during this step. Reacting **17** with 4-methoxyphenylhydrazine hydrochloride in THF, using Cs_2CO_3 as base, furnished the desired pyrazole **18** as the major regioisomer in 3:1 ratio. This crude product was subjected to acid-catalyzed hydrolysis, and the resulting free carboxylic acid was treated with aqueous NaOH in THF to form the sodium salt. A single recrystallization of the crude sodium salt, to our delight, completely rejected the 1,3-regioisomer as well as the minor *R*-stereoisomer, furnishing the drug substance **1** in 63% overall yield and >99% ee. Complete synthesis of **1** was thus achieved in seven steps from commercial starting materials with an overall yield of 33%.

In conclusion, we have developed an efficient, enantioselective route to the CCK 1 antagonist **1**. Efficiency is derived from the concise assembly of the substituted pyrazole structure from a fully elaborated acetylenic ketone, avoiding protecting groups and oxidation−reduction manipulations. The two asymmetric methods, namely, kinetic resolution by enzymatic hydrolysis and the diastereoselective trapping of alkylaryl ketene using (*S*)-ethyl lactate, are very efficient and appear to be suited for large-scale synthesis of the drug substance.

Experimental Section

2-*m*-Tolylpent-4-ynoic Acid Ethyl Ester (3). A 2 L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet, and a thermometer was charged with diisopropyl amine (34.6 mL, 0.246 mol) and anhydrous THF (300 mL). The solution was cooled to 0 °C, and *n*-butyllithium 2.5 M in hexane (100 mL) was added. The solution was stirred for 0.5 h then cooled to −78 °C. Ethyl *m*-tolyl acetate (**2**, 40 mL, 0.224 mol) was added neat to the LDA solution. After stirring for 1 h, propargyl bromide (80 wt % in toluene; 26.8 mL, 0.240 mol) was added dropwise while maintaining the reaction temperature between −75 and −78 °C. The reaction mixture was allowed to slowly warm up to room temperature overnight then quenched with saturated aqueous ammonium chloride (100 mL) and ethyl acetate (100 mL). The layers were separated, and the organic layer was washed with brine (150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to an orange oil. Distillation under reduced pressure furnished 40 g (82%) of ester **3** as a colorless oil. ^{1}H NMR spectrum of the product indicated the presence of about 5% starting material ethyl *m*-tolyl acetate. The product was the further purified by fractional distillation using a vigreux column (8′). The main fraction distilling 83−85 °C/500 mTorr was collected to recover 35 g (72%) of the pure ester **3** as a colorless liquid: $R_f = 0.54$ (hexanes/ethyl acetate, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.19 (m, 1H), 7.11−7.08 (m, 3H), 4.22−4.09 (m, 2H), 3.75 (dd, J = 8.6, 7.1 Hz, 1H), 2.92 (ddd, J = 2.5, 8.6, 16.6 Hz, 1H), 2.61 (ddd, J = 2.5, 7.1, 16.6 Hz, 1H), 2.34 (s, 3H), 1.95 (t, J = 2.5 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 138.4, 137.6, 128.6, 128.5, 128.4, 124.8, 81.6, 69.8, 61.0, 50.8, 23.1, 21.4, and 14.1; HRMS *m*/*z* calcd for $C_{14}H_{17}O_2$ $[M + H]^+$ 217.1223, found 217.1221.

6-(3,4-Dichlorophenyl)-6-oxo-2-*m*-tolylhex-4-ynoic Acid Ethyl Ester (4). A 1 L, one-necked, round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged sequentially with 3,4-dichlorobenzoyl chloride (17.43 g, 0.083 mol) then acetylenic ester **3** (15 g, 0.069 mol) in anhydrous THF (100 mL)

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and anhydrous toluene (100 mL). Catalysts $PdCl_2(PPh_3)_2$ (100 mg, 8.6×10^{-5} mol) and CuI (100 mg, 5.2×10^{-4} mol) were then added followed by *N*-methylmorpholine (15.4 mL, 0.140 mol). The reaction was stirred at room temperature for 14 h when TLC indicated almost complete consumption of starting material. The reaction mixture was quenched with water (100 mL) and ethyl acetate (100 mL) then transferred to a separatory funnel. The layers were separated, and the organic layer was washed twice with water (2×100 mL), brine (50 mL), then dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated to yield **4** as a yellow oil. The crude product was purified by silica gel chromatography (9/1 hexanes/ethyl acetate) to obtain 19 g (69%) of **4** as pale-yellow oil: $R_f = 0.49$ (9/1 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, $J = 2.0$ Hz, 1H), 7.65 (dd, $J = 8.3$, 2.0 Hz, 1H), 7.45 (d, $J = 8.3$ Hz, 1H), 7.29−7.25 (br m, 1H), 7.16−7.13 (m, 3H), 4.25−4.12 (m, 2H), 3.88 (t, $J = 7.83$ Hz, 1H), 3.16 (dd, $J = 17.2$, 7.6 Hz, 1H), 2.98 (dd, $J = 17.2$, 7.8 Hz, 1H), 2.35 (s, 3H), 1.20 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 171.9, 138.7, 138.5, 136.8, 136.3, 133.1, 131.0, 130.5, 128.8, 128.3, 124.8, 94.5, 80.0, 61.4, 49.7, 23.6, 21.3, and 14.0; HRMS *m*/*z* calcd for $C_{21}H_{19}Cl_2O_3$ $[M + H]^+$ 389.1805, found 389.1812.

3-[5-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-*m*-tolyl Propionic Acid Ethyl Ester (5). To a stirred solution of the acetylenic ketone **4** (9.55 g, 0.024 mol) in THF (125 mL) was added Cs_2CO_3 (8.8 g, 0.027 mol) followed by 4-methoxyphenyl hydrazine HCl (6.5 g, 0.037 mol). The resulting slurry reaction mixture was stirred at room temperature overnight then quenched with 1 N HCl until pH 2−3. The contents were transferred to a separatory funnel, and after separation of layers, the aqueous layer was washed with ethyl acetate (3×75 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to an oil. The crude oil was purified by silica gel chromatography (7/3 hexanes/ethyl acetate) to afford 9.46 g (76%) of **5** and 1.74 g (14%) of **7** as dark-orange oils. Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.07 (m, 8H), 6.91−6.86 (m, 3H), 6.21 (s, 1H), 4.22−4.01 (m, 3H), 3.82 (s, 3H), 3.54−3.48 (dd, $J = 14.9$, 9.6 Hz, 1H), 3.11−3.06 (dd, $J = 14.9$, 6.0 Hz, 1H), 2.35 (s, 3H), 1.20−1.16 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.0, 150.9, 140.9, 138.8, 138.2, 132.8, 132.6, 132.2, 130.6, 130.3, 130.2, 128.6, 128.5, 128.1, 127.7, 126.6, 125.0, 114.3, 107.2, 60.8, 55.5, 51.5, 32.3, 21.5, and 14.1; HRMS *m*/*z* calcd for $C_{28}H_{27}Cl_2N_2O_3$ $[M + H]^+$ 509.1393, found 509.1402. Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.91 (d, $J = 1.9$ Hz, 1H), 7.63−7.61 (dd, $J = 8.3$, 2.0 Hz, 1H), 7.45−7.43 (d, $J = 8.4$ Hz, 1H), 7.31−7.26 (m, 1H), 7.21−7.14 (m, 2H), 7.08−7.06 (d, $J = 7.5$ Hz, 1H), 7.00−6.97 (m, 4H), 6.45 (s, 1H), 4.19−4.02 (m, 3H), 3.87 (s, 3H), 3.82−3.79 (m, 1H), 3.46−3.39 (dd, $J = 9.3$, 15.4 Hz, 1H), 2.99−2.94 (dd, $J = 6.2$, 15.4 Hz, 1H), 2.30 (s, 3H), 1.18−1.15 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 159.7, 149.0, 142.9, 138.5, 137.7, 133.5, 132.7, 132.4, 131.4, 130.5, 128.7, 128.5, 128.3, 127.4, 127.3, 124.9, 124.8, 114.5, 102.9, 61.1, 55.6, 51.0, 30.2, 21.4, and 14.1; HRMS *m*/*z* calcd for $C_{28}H_{27}Cl_2N_2O_3$ $[M + H]^+$ 509.1393, found 509.1380

(*S*)-3-[5-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-*m*-tolyl Propionic Acid (10). To a stirred solution of *lipase mucor miehei* (10.0 g) in phosphate buffer pH 7 (500 mL) was slowly added pyrazole ester **5** (15.0 g, 0.029 mol) in IPA (60 mL) for over 30 min to form a slurry. The reaction mixture was monitored every 2 days using chiral HPLC to observe the enantioselective hydrolysis. After 10 days, the reaction mixture was adjusted to pH 1−2 using 1 N HCl then diluted with ethyl acetate (300 mL). The mixture was stirred vigorously for 1 h, then the emulsion was filtered through a pad of Celite. The filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous phase was washed again with ethyl acetate (2×75 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to oil. The crude oil was purified by silica gel chromatography eluting first with 4/1 hexanes/ethyl acetate with 1% methanol to recover 9.0 g (60%, 4/1 *R*/*S*) of the enriched (*R*)-pyrazole ester **11** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.07 (m, 8H), 6.91−6.86 (m, 3H), 6.21 (s, 1H), 4.22−4.01 (m, 3H), 3.82 (s, 3H), 3.54−3.45 (dd, $J = 14.9$, 9.6 Hz, 1H), 3.11−3.06 (dd, $J = 14.9$, 6.0 Hz, 1H), 2.35 (s, 3H), 1.20−1.16 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 159.0, 151.0, 140.9, 138.8, 138.2, 132.8, 132.6, 132.2, 130.6, 130.3, 130.2, 128.6, 128.5, 128.1, 127.7, 126.6, 125.0, 114.3, 107.2, 60.8, 55.5, 51.5, 32.3, 21.5, and 14.1; HRMS *m*/*z* calcd for $C_{28}H_{27}Cl_2N_2O_3$ $[M + H]^+$ 509.1393, found 509.1406. After the enriched (*R*)-pyrazole ester **11** was recovered from the column, the eluent was changed to 1/1 hexanes/ethyl acetate with 2−3% methanol to obtain 5.6 g (40%) of acid **10** as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.09 (m, 8H), 6.91−6.86 (m, 3H), 6.21 (s, 1H), 4.12−4.08 (dd, $J = 9.6$, 5.8 Hz, 1H), 3.82 (s, 3H), 3.54−3.49 (dd, $J = 14.9$, 9.6 Hz, 1H), 3.13−3.08 (dd, $J = 14.9$, 5.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 159.0, 150.6, 141.0, 138.4, 138.2, 132.6, 132.5, 132.2, 130.4, 130.3, 130.2, 128.8, 128.6, 128.4, 127.7, 126.6, 125.1, 114.3, 107.2, 55.5, 51.2, 31.7, and 21.4; HRMS *m*/*z* calcd for $C_{26}H_{23}N_2Cl_2O_3$ $[M + H]^+$ 481.1080, found 481.1084. Anal. Calcd for $C_{26}H_{22}N_2Cl_2O_3$: C, 64.87; H, 4.61; N, 5.82. Found: C, 64.80; H, 4.85; N, 6.0.

(*S*)-Sodium-3-[5-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-*m*-tolyl Propionate (1). To a stirred solution of the pyrazole acid **10** (3.8 g, 0.008 mol) in THF (40 mL) was added NaOH (0.35 g, 0.009 mol) in H_2O (2 mL) at room temperature. The mixture was stirred for 60 min then concentrated to an oil under reduced pressure using a rotary evaporator (30 °C). The oil was diluted in THF (25 mL), and acetonitrile was added whereupon precipitation developed. The solids were stirred for 2 h then filtered, and the solids were washed with acetonitrile to afford 3.34 g (88%) of **1** as a white crystalline solid: mp 280−285 °C; $[\alpha]^{20}_{589}$ +58.8° ($c = 0.1$, EtOH); ^{1}H NMR (500 MHz, D_2O) δ 7.14−7.10 (m, 2H), 6.99−6.96 (t, $J = 7.41$ Hz, 1H), 6.82−6.80 (d, $J = 8.23$ Hz, 2H), 6.74−6.72 (d, $J = 7.41$ Hz, 1H), 6.50−6.40 (m, 4H), 6.22 (d, $J = 7.96$ Hz, 1H), 5.66 (s, 1H), 3.82−3.80 (m, 1H), 3.42 (s, 3H), 3.37−3.28 (m, 2H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.4, 158.6, 152.9, 143.6, 140.0, 136.5, 132.7, 131.4, 131.1, 130.8, 129.8, 128.8, 128.4, 127.6, 126.8, 126.2, 125.2, 114.4, 107.6, 55.5, 54.9, 32.9, and 21.3. Anal. Calcd for $C_{25}H_{21}Cl_2N_2NaO_3$: C, 62.04; H, 4.21; N, 5.57. Found: C, 61.98; H, 4.14; N, 5.43.

Racemization of the Recovered (*R*)-Aryl Propionate Ester 11. 3-[5-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-*m*-tolyl Propionic Acid Ethyl Ester (5). To a stirred solution of the (*R*)-pyrazole ester **11** (13.55 g, 0.026 mol) in EtOH (120 mL) was added potassium ethoxide (5.9 g, 0.029 mol) at room temperature. Racemization was complete after the reaction was stirred overnight. The reaction mixture was quenched with cold H_2O (20 mL), concentrated to quarter volume. The mixture was diluted with ethyl acetate (150 mL) and acidified with 1 N HCl (150 mL). The contents were transferred to a separatory funnel, and the layers were separated. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to oil. The crude oil was purified by silica gel chromatography (4/1 hexanes/ethyl acetate) to afford 12.2 g (90%) of the racemic pyrazole ester **5** as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.07 (m, 8H), 6.91−6.86 (m, 3H), 6.21 (s, 1H), 4.22−4.01 (m, 3H), 3.82 (s, 3H), 3.54−3.48 (dd, $J = 14.9$, 9.6 Hz, 1H), 3.11−3.06 (dd, $J = 14.9$, 6.0 Hz, 1H), 2.35 (s, 3H), 1.20−1.16 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 158.9, 150.9, 140.8, 138.8, 138.2, 132.8, 132.6, 131.1, 130.6, 130.3, 130.2, 128.6, 128.5, 128.1, 127.7, 126.5, 124.9, 114.2, 107.1, 60.7, 55.5, 51.4, 32.3, 21.4, and 14.1; HRMS *m*/*z* calcd for $C_{28}H_{27}Cl_2N_2O_3$ $[M + H]^+$ 509.1393, found 509.1402.

2-*m*-Tolylpent-4-ynoic Acid (13). A 2 L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet, and a thermometer was charged with diisopropyl amine (39.2 mL, 0.280 mol) and anhydrous THF (350 mL). The solution was cooled to 0 °C, and *n*-butyllithium 2.5 M in hexanes (112 mL) was added.

The solution was stirred for 0.5 h then cooled to −78 °C. *m*-Tolyl acetic acid (**12**, 20 g, 0.133 mol) dissolved in 100 mL of THF was added to the LDA solution. After 30 min, 15.8 mL of propargyl bromide (80% in toluene, 0.133 mol) was added slowly to the reaction mixture. After the addition, the reaction mixture was stirred for 2 h at −78 °C and the cold bath removed, allowing the reaction to warm slowly to room temperature. Saturated aqueous ammonium chloride (150 mL) was added to the reaction flask followed by 200 mL of ethyl acetate. The contents were then transferred to a 2 L separatory funnel, and the layers were separated. The organic layer was extracted with brine (50 mL) and dried over anhydrous $MgSO_4$, and after filtration, the solvents were evaporated under reduced pressure to obtain a dark-yellow solid. Recrystallization from hot hexanes afforded the desired carboxylic acid **13** (19.5 g, 78%) as a white crystalline solid: mp 87−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 1H), 7.10 (m, 3H), 3.79 (t, J = 7.96 Hz, 1H), 2.89 (ddd, J = 2.56, 8.36, 19.38 Hz, 1H), 2.59 (ddd, J = 2.60, 6.95, 23.79 Hz, 1H), 2.34 (s, 3H), 1.96 (t, J = 2.54 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 138.5, 136.7, 128.8, 128.7, 128.5, 124.9, 81.1, 70.1, 50.6, 22.5, and 21.4. Anal. Calcd for $C_{12}H_{13}O_2$: C, 76.57; H, 6.43. Found: C, 76.18; H, 6.82.

(*S,S*)-2-*m*-Tolylpent-4-ynoic Acid 1-Ethoxycarbonylethyl Ester (16). A 500 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar was charged the carboxylic acid (**13**, 13 g, 0.069 mol) and 100 mL of dichloromethane. To this solution at room temperature was added 0.1 mL of DMF. Through a pressure equalized addition funnel, 7.3 mL of oxalyl chloride was then added in drops. After stirring at room temperature for 4 h, when a small sample of the reaction mixture on quenching with methanol showed complete formation of the methyl ester, the reaction mixture was evaporated under reduced pressure to obtain the acid chloride **15** as a yellow oil. This crude acid chloride was dissolved in anhydrous toluene (350 mL). Dimethylethylamine (22.3 mL, 0.207 mol) was added, and the reaction mixture was stirred at room temperature. After 30 min, the reaction mixture was cooled to −78 °C, and neat ethyl lactate (8.6 mL, 0.075 mmol) was added. After 1 h, the cooling bath was removed and allowed the reaction to slowly warm up to room temperature. The reaction was quenched with 100 mL of water, and the contents were transferred to a separatory funnel washing the reaction flask with 100 mL of ethyl acetate. The layers were separated, and the combined organic layers were washed with water (3 × 100 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated, and the crude product was purified by filtering through a plug of silica gel (9/1 hexanes/ethyl acetate) to furnish 17.8 g (90%) of the lactate ester **16** as a pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 1H), 7.09 (m, 3H), 5.16 (q, J = 7.01, 14.40 Hz, 1H), 4.05 (q, J = 7.0, 14.40 Hz, 2H), 3.82 (t, J = 8.0 Hz, 1H), 2.90 (ddd, J = 2.83, 8.0, 19.3 Hz, 1H), 2.61 (ddd, J = 2.78, 7.0, 19.4 Hz, 1H), 2.34 (s, 3H), 1.97 (t, J = 2.53 Hz, 1H), 1.41 (d, J = 7.0 Hz, 3H), 1.09 (t, J = 7.33 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.3, 138.2, 136.8, 128.7, 128.5,128.4, 125.0, 81.3, 70.0, 69.2, 61.2, 50.4, 23.1, 21.4, 16.9, and 13.9; HRMS *m*/*z* calcd for $C_{17}H_{21}O_4$ $[M + H]^+$ 289.1434, found 289.1441.

(*S,S*)-6-(3,4-Dichlorophenyl)-6-oxo-2-*m*-tolylhexynoic Acid 1-Ethoxycarbonylethyl Ester (17). A 1 L, one-necked, round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged sequentially with 3,4-dichlorobenzoyl chloride (14.32 g, 0.684 mol) then acetylenic ester (**16**, 16.5 g, 0.057 mol) in anhydrous THF (75 mL) and anhydrous toluene (75 mL). Catalysts $PdCl_2(PPh_3)_2$ (100 mg, 8.6×10^{-5} mol) and CuI (100 mg, 5.2×10^{-4} mol) were then added followed by *N*-methylmorpholine (15.0 mL, 0.138 mol). The reaction mixture was stirred at room temperature for 14 h when TLC indicated almost complete consumption of the starting material. The reaction was quenched with water (100 mL) and ethyl acetate (100 mL), and the contents were transferred to a separatory funnel. The layers were separated, and the organic layer was washed with water (2 × 100 mL), brine (1 × 50 mL), and then dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure to yield the acetylenic ketone **17** as yellow oil. The crude product was purified by filtering through a plug of silica gel (9/1 hexanes/ethyl acetate) to obtain **17** as a pale-yellow oil (21 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 1.9 Hz, 1H), 7.64 (dd, J = 1.9, 8.3 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.28 (m, 1H), 7.15 (m, 3H), 5.13 (q, J = 7.08, 14.3 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.97 (t, J = 7.7 Hz, 1H), 3.2 (dd, J = 7.3, 17.3 Hz, 1H), 3.0 (dd, J = 8.0, 17.4 Hz, 1H), 2.35 (s, 3H), 1.47 (d, J = 7.1 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 171.2, 170.0, 138.6, 138.5, 136.2, 136.1, 133.2, 131.1, 130.6, 128.9, 128.8, 128.7, 128.4, 125.0, 94.2, 80.1, 69.5, 61.3, 49.5, 23.7, 21.4, 16.8, and 13.9; HRMS *m*/*z* calcd for $C_{24}H_{23}O_5Cl_2$ $[M + H]^+$ 461.0917, found 461.0905.

(*S,S*)-3[5-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-*m*-tolylpropanoic Acid 1-Ethoxycarbonylethyl Ester (18). To a stirred solution of the acetylenic ketone **17** (15.5 g, 0.033 mol) in THF (150 mL) was added Cs_2CO_3 (12 g, 0.036 mol) followed by 4-methoxyphenyl hydrazine HCl (6.5 g, 0.037 mol). The slurry reaction mixture was stirred at room temperature overnight then slowly quenched with 1 N HCl until pH 2−3. The contents were transferred to a separatory funnel, and the layers were separated. The aqueous layer was washed with ethyl acetate (3 × 75 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to an oil. The crude oil was purified by filtering through a plug of silica gel (8.5/1.5 hexanes/ethyl acetate) to furnish a mixture of regioisomeric pyrazole esters as a dark orange oil (18.6 g, 95%; 74% 1,5-regioisomer and 26% 1,3-regioisomer based on ^{1}H NMR). This regioisomeric mixture was used in the next step with out any further purification. A small sample of pure **18** was obtained by silica gel flash column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.13 (m, 8H), 6.85 (m, 3H), 6.23 (s, 1H), 5.10 (q, J = 7.08, 14.3 Hz, 1H), 4.05 (m, 2H), 3.82 (s, 3H), 3.49 (dd, J = 9.3, 14.7 Hz, 1H), 3.10 (dd, J = 6.1, 14.7 Hz, 1H), 2.35 (s, 3H), 1.43 (d, J = 7.04 Hz, 3H), 1.08 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.4, 159.0, 150.7, 140.9, 138.1, 138.0, 132.8, 132.6, 132.2, 130.6, 130.3, 130.2, 128.9, 128.4, 128.2, 127.7, 126.6, 125.1, 114.3, 107.3, 69.0, 61.2, 55.5, 51.1, 32.2, 21.5, 16.9, and 13.9; HRMS *m*/*z* calcd for $C_{31}H_{31}N_2O_5Cl_2$ $[M + H]^+$ 581.1605, found 581.1617.

(*S*)-Sodium-3-[5-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-*m*-tolyl Propionate (1). The crude lactate ester (18 g, 74% **18**) obtained as described above was dissolved in 150 mL of acetic acid. Hydrochloric acid (2 N, 25 mL) was added, and the reaction mixture was stirred at 85 °C for 4 h when TLC showed complete hydrolysis. After cooling to room temperature, the contents were transferred to a separatory funnel and diluted with ethyl acetate (250 mL) and water (50 mL). The layers were separated, and the organic layer was washed with water (3 × 50 mL), brine, and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated under reduced pressure to obtain a brown oil (15 g, 98%). The crude acid was dissolved in THF (150 mL), and the solution was cooled to 0 °C. Concentrated aqueous sodium hydroxide (1.26 g in 10 mL of water) was added, and the reaction mixture was stirred for 2 h. The ice bath was removed, and after warming to room temperature, the solvents were evaporated. The crude sodium salt thus obtained was redissolved in anhydrous THF (100 mL), and 100 mL of acetonitrile was added. On stirring at room temperature, precipitation of the sodium salt began slowly. After 4 h, the mixture was filtered, washing the solids with 1:1 THF/acetonitrile. The white solids were collected and dried under house vacuum to obtain 10 g of the desired sodium salt **1** as white crystalline solid (63% overall yield, 99.9% ee): mp 280−285 °C; $[\alpha]^{20}_{589}$ +58.8° (c = 0.1, EtOH).

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Supporting Information Available: General experimental procedures and details of the preparation of **1** by the first-generation route are provided as supplemental information. Copies of ^{1}H and ^{13}C NMR spectra of all new, isolated compounds are also provided. This material is available free of charge via Internet at http://pubs.acs.org.

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