Organic Process Research & Development **2001**, *5*, 587−592

The Synthesis of a Selective PDE_4/TNFα Inhibitor

Stéphane Caron* and Enrique Vazquez†

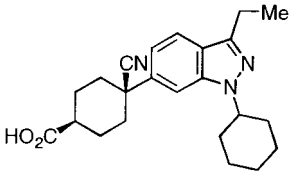
Process Research, Chemical Research and Development, Pfizer Global Research and Development, Groton, Connecticut 06340-8156, U.S.A.

Abstract:

Two syntheses of *cis*-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid (1), a selective PDE_4/TNFα inhibitor are described. The first synthesis relied on a solvolysis of a tertiary benzylic alcohol to the nitrile using TMSCN and on the epimerization of an ester to its thermodynamically favored position prior to its hydrolysis. It was demonstrated that the selectivity was controlled by the rate of hydrolysis of the two diastereomeric esters. The second synthesis proved to be more efficient and used a novel nucleophilic aromatic substitution of a fluoroindazole with the anion of a tertiary nitrile. Another key element of the route was a selective Pinner reaction of a secondary nitrile in the presence of a tertiary nitrile.

Introduction

Cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid (**1**) is a PDE_4/TNFα inhibitor for the treatment of inflammatory diseases which was recently discovered and nominated for development at Pfizer Global Research and Development.[1] Structurally, the compound presents the interesting challenge of generating a tertiary benzylic nitrile on a 1,4-disubstituted cyclohexane with the appropriate control of the relative stereochemistry of a carboxylic acid, and also offered the opportunity for the development of new methodology for the construction of 6-substituted indazoles. Our goal was to find a safe and cost-effective synthesis for the preparation of **1**.



(**1**)

In this article, we report two different approaches for the synthesis of this drug candidate.

Results and Discussion

We originally hoped that the requisite carboxylic acid stereochemistry could be obtained by epimerization of an ester to its thermodynamically favored equatorial position.[2] This approach relied on the establishment of the desired tertiary nitrile by solvolysis of a tertiary benzylic alcohol which would arise from the addition of an arylmetal species to a cyclohexanone.

We first developed an efficient synthesis of the desired bromoindazole **2** starting from 3-bromophenol (**3**),[3] and studied the halogen−metal exchange and addition to 4-oxocyclohexanecarboxylic acid ethyl ester (**4**).[4] In our initial attempt, the aryllithium was generated using *n*-BuLi in THF at −78 °C and the resulting anion was added to a THF solution of **4** cooled to −78 °C, affording esters **5** as a mixture of diastereoisomers in 64% yield along with 35% of the protonated indazole **6**. Trapping experiments using benzaldehyde afforded a quantitative yield of the desired adduct showing that indazole **6** originated from the enolization of **4** in our previous experiment. Furthermore, we found that the generation of the lithium species had to be performed below −50 °C to avoid decomposition of the anion. Formation of the organomagnesium and organocerium[5] reagents or the presence of additives such as $MgBr_2$ or *n*-Bu_4NI[6,7] did not improve the reaction. Generation of the anion in DME, MTBE, diisopropyl ether, toluene, or xylenes also proved to be difficult. Fortunately, we found that preparation of the lithium anion in toluene in the presence of 2 equiv of THF allowed for the formation of the diastereomeric mixture of esters **5** in 84% yield containing only 16% indazole **6**.[8] However, it was necessary to rely on a chromatographic separation for the removal of **6**. Interestingly, the reaction had to be quenched below 0 °C to avoid the conversion of the esters **5** to lactone **7**. (Scheme 1)

The next step was the conversion of the tertiary benzylic alcohol to a nitrile. It is precedented that the reaction of 1-phenylcyclohexanol with TMSCN (2−3 equiv) in the presence of $SnCl_4$ (1.5 equiv) leads to formation of the nitrile[9] and that the conversion of substituted cyclobutanols to the corresponding nitriles also proceeds using either BF_3·Et_2O or ZnI_2.[10] We found that $SnCl_4$ was the optimal Lewis acid

* Author for correspondence. E-mail: stephane_caron@groton.pfizer.com. Telephone: (860) 441-3103. Fax (860) 441-3630.

† Current address: Merck & Co. Inc., RY-800-C367, P.O. Box 2000, Rahway, NJ 07065-0900.

(1) Marfat, A. and Damon, D. B. Manuscript in preparation.

(2) Nakazaki, M.; Isoe, S. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 1198−1204.

(3) Caron, S.; Vazquez, E. *Synthesis* **1999**, 588−592.

(4) Although the desired ketone is commercially available, we found that material of higher quality was obtained by oxidation of the corresponding alcohol with TEMPO and bleach prior to the condensation. See: de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153−1174.

(5) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233−4236.

(6) Richey, H. G.; DeStephano, J. P. *J. Org. Chem.* **1990**, *55*, 3281−3286.

(7) Chastrette, M.; Amouroux, R. *J. Chem. Soc., Chem. Commun.* **1970**, 470−471.

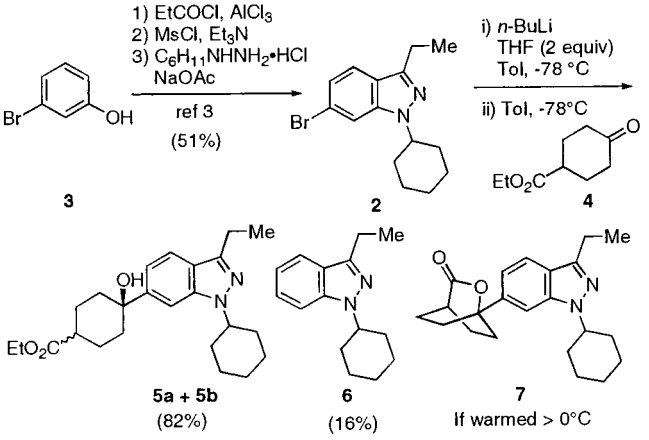
(8) Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335−2348.

(9) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331−6342.

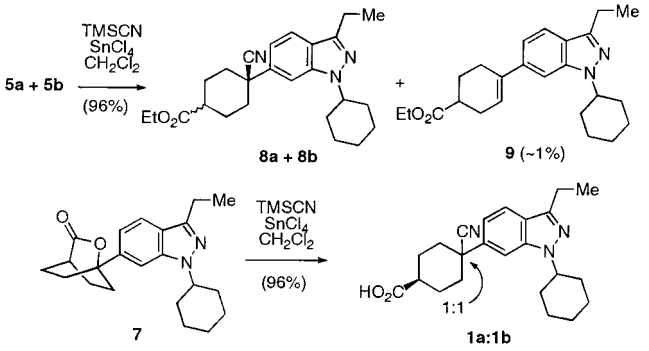
(10) Kobayashi, K.; Kanno, Y.; Seko, S.; Suginome, H. *J. Chem. Soc., Perkin Trans. 1* **1992**.

10.1021/op010223p CCC: $20.00
Published on Web 10/03/2001

Scheme 1



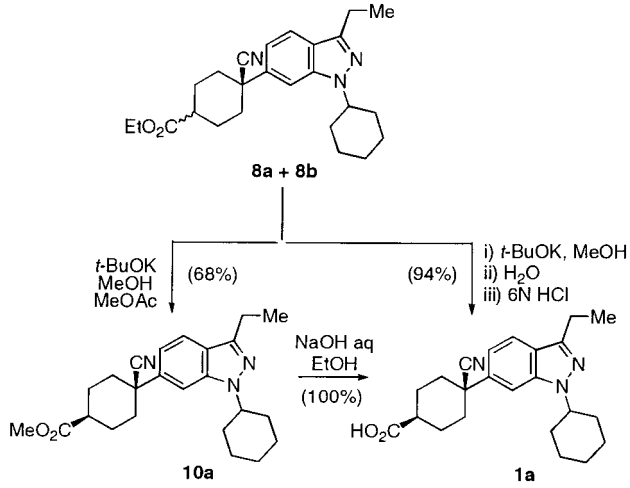
Scheme 2



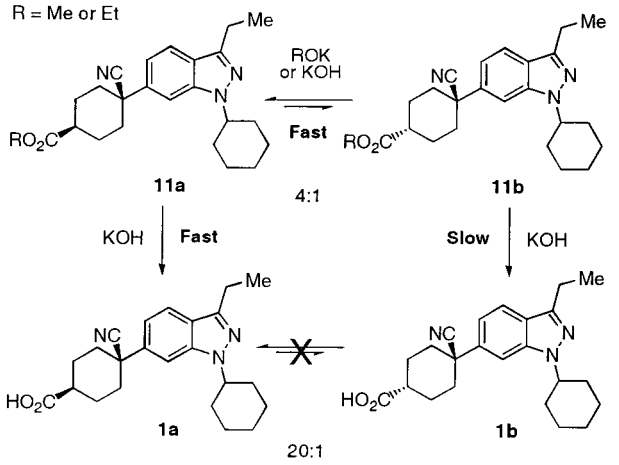
in our case and that it could be used catalytically. The conversion of ester **5a** and **5b** to a diastereomeric mixture of nitriles **8a** and **8b** was accomplished by using TMSCN (5 equiv) and $SnCl_4$ (0.25 equiv) in CH_2Cl_2 in near quantitative yield. The excess of TMSCN proved to be necessary in order to minimize the generation of alkene **9** (about 1% of **9** was obtained using our protocol). Other Lewis acids were studied (BF_3•Et_2O, BCl_3, $ZnCl_2$, $AlCl_3$, $AlCl(OiPr)_2$, $Al(OiPr)_3$, $TiCl_4$) but none were as effective as $SnCl_4$. Subjection of lactone **7** to these conditions generated the tertiary carbocation as an intermediate since it provided a 1:1 mixture of diastereomeric carboxylic acids (**1a** and **1b**) which could not be epimerized to the desired diastereomer. (Scheme 2)

We next explored the isomerization of the mixture of ethyl esters and discovered that treatment of **8a** and **8b** with *t*-BuOK in methanol in the presence of MeOAc (in order to scavenge any KOH present) allowed for the selective crystallization of a single diastereomer of methyl ester **10a**. Hydrolysis of **10a** could be accomplished without noticeable epimerization upon treatment with aqueous NaOH in EtOH**.** More importantly, we found that rather than isolating methyl ester **10a**, slow addition of water to the reaction mixture during the epimerization provided carboxylic acid **1** directly in greater than 20:1 diastereoselectivity and 94% yield. (Scheme 3) We demonstrated that epimerization of the esters **11a** and **11b** (as a mixture of methyl and ethyl esters) was achieved (about 4:1 ratio at equilibrium in EtOH)[11] and that

Scheme 3



Scheme 4



hydrolysis of the desired equatorial ester proceeded at a greater rate than the axial one. Since **11a** and **11b** are in a rapid equilibrium, the rate of hydrolysis dictates the final ratio of **1a** and **1b** as we confirmed that epimerization of the corresponding carboxylate did not occur under the reaction conditions.[12] (Scheme 4)

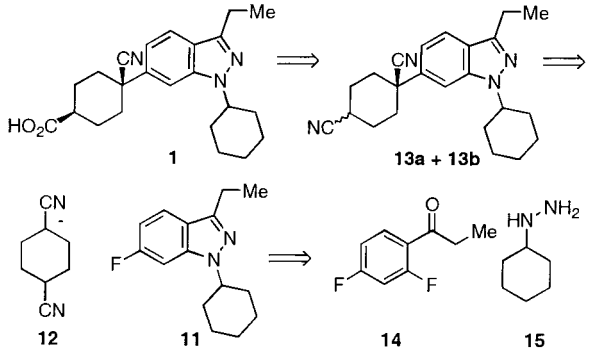
While our original synthesis of **1** proved to be efficient (six steps, 38% overall yield from 3-bromophenol), it suffered from several drawbacks regarding its feasibility on large scale. First, the halogen metal exchange and addition to ketone **4** appeared to be too capricious to become a robust process and required a chromatographic purification. Second, the use of TMSCN would not be preferable on larger scale, although it suited our needs to provide kilogram quantities of nitrile **8**. Finally, all intermediates proved to be oils, which made isolations difficult and left no room for purification by crystallization. Although the HBr salt of bromoindazole **2** could be prepared, it proved to be a weak salt and difficult to handle. These issues forced us to seek a better alternative for the long-term preparation **1**.

An appealing approach for the synthesis of **1** was the nucleophilic aromatic substitution of a fluoroindazole **11** with the anion of a 1,4-dicyanocyclohexane **12** followed by a

(11) Eliel, E. L.; Haubenstock, H.; Acharya, R. V. *J. Am. Chem. Soc.* **1961**, *83*, 2351−2354.

(12) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42−48.

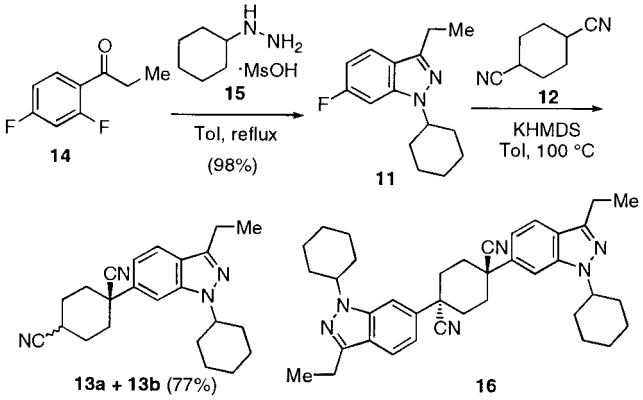
Scheme 5



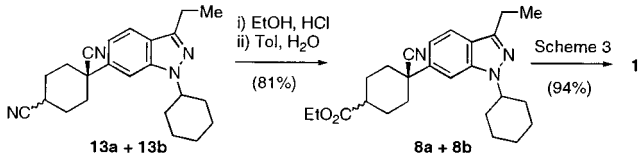
selective hydrolysis of the secondary nitrile of compound **13** through a Pinner reaction.[13] Although it appeared that there was no precedent for the addition of a nitrile anion to an arene not containing strong electron-withdrawing groups prior to our work, we chose to investigate this potential route as it presented several advantages, especially the elimination of TMSCN as a reagent. We hoped that formation of fluoroindazole **11** would be achieved from difluoropropiophenone **14** and cyclohexylhydrazine **15,**[14] using lower temperatures than required with the mesylate in our first synthesis of **2** (Scheme 1). The high level of convergency in the proposed synthesis was also attractive since it required three simple starting materials: 2,4-difluoropropiophenone (**14**), 1,4-dicyanocyclohexane (**12**),[15] and cyclohexylhydrazine (**15**). (Scheme 5)

We were pleased to find that reaction between difluoropropiophenone **14** and the mesylate salt of cyclohexylhydrazine (**15**)[16] in the presence of sodium acetate in refluxing toluene and removing water with a Dean−Stark apparatus occurred rapidly and resulted in a 98% yield of indazole **11**. Although indazole **11** was an oil, the purity was sufficiently high to carry on in the next step which we found proceeded best in toluene. Since toluene distillation provides an efficient azeotrope with water, concentration of the toluene solution containing fluoroindazole **11** assured us of anhydrous conditions for our key nucleophilic aromatic substitution. As previously communicated in the description of our methodology,[17] the use of 1.5 equiv of KHMDS in toluene at 100 °C proved to be optimal for the coupling of fluoroindazole **11** with 1,4-dicyanocyclohexane **12** (4 equiv), providing a mixture of diastereomeric nitriles **13a** and **13b** (77%). The major impurity resulting from this process proved to be dimer **16** which was generated in approximately 5% as a single diastereomer and could be removed by crystallization from methanol to a level below 1%. Although dinitrile **13a** and **13b** could be separated by chromatography, the crude mixture of diastereomers was usually taken on directly to the hydrolysis of the nitrile. (Scheme 6)

Scheme 6



Scheme 7



To the best of our knowledge, the selective hydrolysis of a secondary nitrile in the presence of a tertiary nitrile is unprecedented. Our initial attempt, using methanol saturated with HCl, proved to be encouraging since only the desired product as well as the dimethyl ester, were generated in about equal amounts. This result led us to believe that a more hindered alcohol could increase selectivity. Indeed, when we used ethanol, none of the undesired diethyl ester was observed. We found that formation of the imidate hydrochloride using ethanol with HCl gas and its hydrolysis (toluene/H_2O) provided the desired ethyl ester **8a** and **8b** in 81% yield. Final hydrolysis of the ester to **1** could be accomplished as discussed previously (Scheme 7).

Conclusions

The second route to our synthetic target **1** proved to be very efficient since the molecule was assembled in four steps and 57% overall yield from 2,4-difluoropropiophenone (**14**). Furthermore, the synthesis no longer required cryogenic or high temperature (>130 °C) reactions and could be amenable to multikilogram scale. The process research work on **1** allowed for the development of new methodologies, namely a two-step synthesis of indazoles from phenols, the nucleophilic aromatic substitution of secondary nitriles with aryl fluorides using KHMDS as a base, as well as the demonstration of the selective hydrolysis of a secondary nitrile in the presence of a tertiary nitrile.

Experimental Section

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Silica gel chromatography was carried out with J.T. Baker 40 mm silica gel according to Still's procedure.[18] Thin-layer chromatography was performed with EM Separations Technology silica gel F_{254}, HPLC was performed with

(13) Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 179−211.
(14) Villalobos, A.; Blake, J. F.; Biggers, C. K.; Butler, T. W.; Chapin, D. S.; Chen, Y. L.; Ives, J. L.; Jones, S. B.; Liston, D. R.; Nagel, A. A.; Nason, D. M.; Nielsen, J. A.; Shalaby, I. A.; White, W. F. *J. Med. Chem.* **1994**, *37*, 2721−2734.
(15) Malachowski, R.; Jankiewicz, J. W.; Jozkiewicz, S. *Chem. Ber.* **1938**, *71*, 759−767.
(16) Ghali, N. I.; Venton, D. L.; Hung, S. C.; Le Breton, G. C. *J. Org. Chem.* **1981**, *46*, 5413−5414.
(17) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712−713.
(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

a Hewlett-Packard Series 1100 using a Puresil C_{18} column (4.6 mm × 150 mm) and 50/50 or 80/20 CH_3CN/H_2O mobile phase. Melting points were measured in open capillary tubes and are uncorrected. ^1H (400 MHz) and ^{13}C NMR (100 MHz) were measured in $CDCl_3$ unless otherwise indicated. IR spectra were recorded as thin films on NaCl plates unless otherwise indicated.

6-Bromo-1-cyclohexyl-3-ethyl-1H-indazole (2). Methanesulfonic acid 5-bromo-2-propionyl-phenyl ester[3] (36.6 g, 119 mmol) was combined with cyclohexylhydrazine (**16**) (27.2 g, 238 mmol) and NH_4OAc (23.0 g, 299 mmol) in xylenes (220 mL). The reaction mixture was heated to 135 °C in a Dean−Stark apparatus for 48 h. The reaction was cooled to room temperature and concentrated to a low volume under reduced pressure. The crude product was filtered through a pad of silica gel (ratio product/silica gel 1/5) eluting first with hexanes and then with a 10/90 mixture of EtOAc and hexanes to yield 28.0 g of 6-bromo-1-cyclohexyl-3-ethyl-1H-indazole (**2**) (76% yield) after concentration.^1H NMR δ 1.35 (t, 3, J = 7.7), 1.39−2.06 (m, 10), 2.95 (q, 2, J = 7.7), 4.21−4.28(m, 1), 7.15 (d, 1, J = 8.5), 7.51 (d, 1, J = 8.5), 7.56 (s, 1). ^{13}C NMR δ 13.95, 20.50, 25.35, 25.84, 32.44, 58.15, 112.01, 120.10, 121.37, 121.65, 122.82, 140.37, 146.60. IR 2934, 2855, 1606, 1502, 1451, 1048, 951, 834 cm^{-1}. Analysis calculated for $C_{15}H_{19}BrN_2$: C, 58.64; H, 6.23; N, 9.12. Found: C, 58.82; H, 6.20; N, 9.01.

4-(1-Cyclohexyl-3-ethyl-1H-indazol-6-yl)-4-hydroxy-cyclohexanecarboxylic Acid Ethyl Ester (5a + 5b). To a solution of 6-bromo-1-cyclohexyl-3-ethyl-1H-indazole (**2**) (12.7 g, 41.3 mmol) in toluene (64 mL) was added THF (6.70 mL, 82.6 mmol). The solution was cooled to −78 °C, and *n*-butyllithium (17.3 mL of a 2.5 *M* solution in hexanes, 43.4 mmol) was added dropwise. The solution was stirred 10 min and added to a solution of 4-oxo-cyclohexanecarboxylic acid ethyl ester (**4**) (8.80 g, 51.7 mmol) in toluene (127 mL) at −78 °C. The reaction mixture was stirred 15 min and poured into 1 N aqueous HCl (200 mL). The layers were separated, and the aqueous layer was extracted with toluene (60 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to an oil which was purified by filtration through a pad of silica gel eluting with 4:1 hexanes/EtOAc. The product-rich fractions were concentrated to yield 4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-4-hydroxy-cyclohexanecarboxylic acid ethyl ester (**5**) (13.5 g, 82%) as a mixture of diastereoisomers. Upon standing, one of the diastereoisomers crystallized and was triturated with hexanes (*cis* diastereoisomer **5a**): mp = 118−120 °C. ^1H NMR δ 1.25−1.40 (m, 4), 1.27 (t, 3, J = 7.1), 1.35 (t, 3, J = 7.7), 1.65−2.07 (m, 15), 2.37−2.44 (m, 1), 2.96 (q, 2, J = 7.7), 4.15 (q, 2, J = 7.1), 4.30−4.38 (m, 1), 7.13 (d, 1, J = 8.5), 7.58 (s, 1), 7.63 (d, 1, J = 8.5). ^{13}C NMR δ 14.16, 14.26, 20.69, 24.60, 25.39, 25.91, 32.54, 38.22, 42.57, 57.59, 60.34, 72.80, 104.49, 116.80, 120.28, 121.26, 139.84, 146.09, 146.93, 175.63. IR 3504, 2937, 1715, 1372, 1258, 1221, 1042, 976 cm^{-1}. Analysis calculated for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 72.11; H, 8.55; N, 6.92. An X-ray single-crystal structure was obtained on ester **5a** and appears in the Supporting Information.[19]

4-Cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic Acid Ethyl Ester (8a + 8b). To solution of 4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-4-hydroxy-cyclohexanecarboxylic acid ethyl ester (**5a** + **5b**) (13.5 g, 33.9 mmol) in CH_2Cl_2 (135 mL) cooled to 0 °C was added trimethylsilyl cyanide (22.6 mL, 169 mmol) followed by a slow addition of $SnCl_4$ (13.6 mL of a 1.0 *M* solution in CH_2Cl_2, 13.6 mmol). The reaction mixture was allowed to warm to room temperature overnight. K_2CO_3 (18.7 g, 136 mmol) and $KF{\cdot}2H_2O$ (12.8 g, 136 mmol) were added, followed by dropwise addition of H_2O (4.30 mL, 239 mmol). The reaction mixture was stirred vigorously for 90 min, after which silica gel (25 g) was added. The mixture was filtered and washed thoroughly with CH_2Cl_2. The filtrate was washed with saturated aqueous $NaHCO_3$ (250 mL), dried over $MgSO_4$, filtered, and concentrated to an oil to yield 13.2 g (96% recovery) of 4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid ethyl ester (**8**) as a mixture of diastereoisomers. For characterization purposes, a sample of each diastereoisomer was obtained by chromatographic purification on silica gel eluting with 4:1 hexanes/EtOAc. Higher R_f diastereoisomer (*cis* diastereoisomer): ^1H NMR δ 1.28 (t, 3, J = 7.1), 1.36 (t, 3, J = 7.7), 1.43−1.56 (m, 2), 1.74−1.77 (m, 2), 1.93−2.10 (m, 10), 2.20−2.24 (m, 2), 2.31 (d, 2, J = 12.9), 2.30 (tt, 1, J = 12.2, 3.5), 2.95 (q, 2, J = 7.7), 4.15 (q, 2, J = 7.1), 4.29−4.37 (m, 1), 7.13 (d, 1, J = 8.5), 7.52 (s, 1), 7.68 (d, 1, J = 8.5). ^{13}C NMR δ 14.06, 14.23, 20.62, 25.35, 25.81, 26.20, 32.57, 36.77, 42.15, 44.27, 57.67, 60.63, 106.08, 116.96, 121.22, 121.95, 122.19, 138.23, 139.61, 146.31, 174.30. IR: 2933, 2856, 2231, 1732, 1189, 1041, 810 cm^{-1}. Analysis calculated for $C_{25}H_{33}BrN_3O_2$: C, 73.68; H, 8.15; N, 10.31. Found: C, 73.58; H, 8.28; N, 10.38. Lower R_f diastereoisomer (*trans* diastereoisomer): mp = 89−91 °C. ^1H NMR δ 1.26 (t, 3, J = 7.1), 1.33 (t, 3, J = 7.7), 1.40−1.54 (m, 2), 1.71−1.78 (m, 2), 1.89−2.19 (m, 13), 2.23−2.31 (m, 2), 2.94 (q, 2, J = 7.7), 4.17 (q, 2, J = 7.1), 4.26−4.33 (m, 1), 7.10 (d, 1, J = 8.5), 7.47 (s, 1), 7.64 (d, 1, J = 8.5). ^{13}C NMR δ 14.07, 14.29, 24.71, 25.35, 25.80, 32.58, 33.74, 37.57, 44.26, 57.59, 60.59, 106.05, 117.26, 121.16, 121.85, 122.61, 138.42, 139.60, 146.27, 174.47. IR: 2973, 2939, 2861, 2233, 1721, 1452, 1206, 1185, 1169, 813 cm^{-1}. Analysis calculated for $C_{25}H_{33}BrN_3O_2$: C, 73.68; H, 8.15; N, 10.31. Found: C, 73.62; H, 8.53; N, 10.30.

4-Cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic Acid Methyl Ester (10a + 10b). To solution of 4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid ethyl ester (**8**) (1.80 g, 4.42 mmol) in MeOH (5.4 mL) containing MeOAc (0.35 mL, 4.40 mmol) was added *t*-BuOK (1.50 g, 13.4 mmol) in portions at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The mixture was cooled to 0 °C and filtered, and the solids were washed with MeOH and dried under vacuum to afford 4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxy-

(19) The author has deposited atomic coordinates for structures **5a**, **13a**, and **13b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director Cambridge Crystallographic Data Centre 12 Union Road Cambridge CB2 1EZ UK.

lic acid methyl ester (**10a**) as a single diastereomer (1.20 g, 68%): mp 158−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, 3, J = 7.7), 1.42−1.54 (m, 2), 1.74−1.78 (m, 1), 1.92−2.20 (m, 11), 2.22 (dd, 2, J = 13.9, 2.7), 2.31 (d, 2, J = 12.5), 2.42 (tt, 1, J = 12.1, 3.5), 2.98 (q, 2, J = 7.7), 3.72 (s, 3), 4.30−4.37 (m, 1), 7.13 (d, 1, J = 8.5), 7.52 (s, 1), 7.68 (d, 1, J = 8.5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.06, 20.62, 25.35, 25.82, 26.20, 32.58, 36.73, 42.02, 44.25, 51.89, 57.67, 106.08, 116.97, 121.23, 121.96, 122.18, 138.19, 139.61, 146.31, 174.73. IR: 2939, 2859, 2237, 1730, 1621, 1461, 1452, 1320, 1264, 1170, 1039 cm^{-1}. Analysis calculated for $C_{24}H_{31}N_3O_2$: C, 73.25; H, 7.94; N, 10.68. Found: C, 72.95; H, 8.15; N, 10.61.

***cis*-4-Cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic Acid (1).** To a solution of 4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid methyl ester (**10**) (5.00 g, 12.7 mmol) in EtOH (25 mL) was added 10% aqueous NaOH (25 mL). The mixture was stirred overnight and cooled to 0 °C before addition of 6 N HCl (14 mL). A white solid precipitated, the mixture was stirred for 15 min, and the solids were filtered, washed with H_2O, and dried under vacuum to afford *cis*-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid (**1**) (4.82 g, 100%). The acid had identical spectroscopic and physical properties of the compound prepared from the direct hydrolysis described below.

***cis*-4-Cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic Acid (1).** To a solution of crude 4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid ethyl ester (**8**) (3.51 g, 8.61 mmol) in MeOH (130 mL) was added *t*-BuOK (2.90 g, 25.8 mmol). The solution was stirred at room temperature 10 h, and H_2O (3.50 mL, 194 mmol) was added. The reaction mixture was stirred until complete disappearance of the starting material (14 h). Most of the methanol was distilled off, H_2O was added (10 mL) followed by addition of 6 N HCl until pH = 2. The solid was triturated for 90 min, filtered, and dried under vacuum to afford *cis*-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid (**1**) (3.00 g, 94%). ^{1}H NMR δ 1.34 (t, 3, J = 7.9), 1.42−1.51 (m, 2), 1.74 (d, 1, J = 12.9), 1.90−2.13 (m, 11), 2.23−2.33 (m, 4), 2.46 (tt, 1, J = 12.0, 3.5), 2.96 (q, 2, J = 7.9), 4.28−4.36 (m, 1), 7.13 (dd, 1, J = 8.5, 1.3), 7.67 (d, 1, J = 8.3). ^{13}C NMR δ 13.97, 20.47, 25.27, 25.76, 25.91, 32.47, 36.57, 41.64, 44.14, 57.70, 106.05, 116.96, 121.25, 121.88, 122.01, 138.15, 139.53, 146.34, 179.80. IR: 3504, 3788−2866 (br), 2236, 1726, 1621, 1453, 1254, 1171, 964, 814 cm^{-1}. Analysis calculated for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.60; H, 7.63; N, 10.95.

1-Cyclohexyl-3-ethyl-6-fluoro-1H-indazole (11). To a solution of 1-(2,4-difluoro-phenyl)-propan-1-one (**14**) (21.29 g, 125.1 mmol) in toluene (120 mL) was added NaOAc (26.75 g, 326.1 mmol) and cyclohexylhydrazine mesylate (**15**) (34.0 g, 163 mmol). The reaction mixture was heated to reflux in a Dean−Stark apparatus for 12 h. The reaction was cooled to room temperature and poured into 1 N HCl (100 mL). The toluene layer was separated and washed with H_2O (75 mL) and brine (75 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 30.07 g of 1-cyclohexyl-3-ethyl-6-fluoro-1H-indazole (**11**) (98% yield). ^{1}H NMR δ 1.33 (t, 3, J = 7.7), 1.35−1.44 (m, 2), 1.47−1.96 (m, 8), 2.93 (q, 2, J = 7.7), 4.14−4.22 (m, 1), 6.81 (dt, 1, J = 8.9, 2.1), 6.99 (dd, 1, J = 9.8, 2.1), 7.40 (ddd, 1, J = 8.7, 5.2, 0.4). ^{13}C NMR δ 13.97, 20.53, 25.37, 25.84, 32.32, 58.18, 94.77 (d, J = 27.4), 109.11 (d, J = 26.0), 119.38, 121.75 (d, J = 11.5), 139.89 (d, J = 13.0), 146.61, 161.95 (d, J = 242). IR: 2968, 2934, 2856, 1624, 1507, 1174, 1125, 825 cm^{-1}. Analysis calculated for $C_{15}H_{19}FN_2$: C, 73.14; H, 7.77; N, 11.37. Found: C, 73.33; H, 7.90; N, 11.46.

1-(1-Cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexane-1,4-dicarbonitrile (13a + 13b). To a solution of 1-cyclohexyl-3-ethyl-6-fluoro-1H-indazole (**11**) (1.50 g, 6.09 mmol) and cylohexane-1,4-dicarbonitrile (**12**) [15] (3.27 g, 24.4 mmol) in toluene (15 mL) was added KHMDS (1.82 g, 9.12 mmol). The reaction mixture was heated to 100 °C, stirred for 5 h, cooled to room temperature and poured into 1 N HCl (15 mL). The layers were separated, and the organic extracts were concentrated. The crude product was stirred in 20% EtOAc/hexanes (15 mL) for 20 min, and the solids were filtered (1.1 g of cylohexane-1,4-dicarbonitrile (**12**) recovered). The filtrate was concentrated to a crude oil. For characterization purposes, the diastereoisomers were obtained by purification by chromatography on silica gel (125 g) eluting with 2:1 hexanes/EtOAc (1.69 g of product isolated, 77% yield). Higher R_f diastereoisomer (*trans*-dinitrile diastereoisomer **13a**): mp = 140−142 °C. ^{1}H NMR δ 1.37 (t, 3, J = 7.7), 1.24−1.78 (m, 4), 1.92−2.10 (m, 6), 2.19−2.35 (m, 8), 2.98 (q, 2, J = 7.7), 3.15−3.17 (m, 1), 4.30−4.39 (m, 1), 7.19 (dd, 1, J = 8.5, 1.7), 7.51 (d, 1, J = 0.8), 7.71 (d, 1, J = 8.5). ^{13}C NMR δ 14.07, 20.60, 25.34, 25.79, 25.92, 32.61, 33.36, 44.30, 57.66, 105.92, 117.04, 121.00, 121.52, 121.79, 122.09.137.33, 139.54, 146.41. IR: 2934, 2239, 1620, 1448, 1435, 1238, 1049, 803 cm^{-1}. Analysis calculated for $C_{25}H_{28}N_4$: C, 76.63; H, 7.83; N, 15.54. Found: C, 76.69; H, 7.87; N, 15.65. Lower R_f diastereoisomer (*cis*-dinitrile diastereoisomer **13b**): mp = 136−138 °C. ^{1}H NMR δ 1.36 (t, 3, J = 7.7), 1.42−1.53 (m, 2), 1.74−1.82 (m, 2), 1.89−2.08 (m, 8), 2.17−2.34 (m, 6), 2.58 (tt, 1, J = 12.2, 3.5), 2.97 (q, 2, J = 7.7), 4.28−4.36 (m, 1), 7.09 (dd, 1, J = 8.5, 1.7), 7.49 (d, 1, J = 1.0), 7.69 (d, 1, J = 8.5). ^{13}C NMR δ 14.02, 20.57, 25.32, 25.81, 27.07, 27.27, 32.57, 36.04, 43.63, 57.75, 106.05, 116.65, 121.17, 121.50, 122.13, 137.17, 139.54, 146.38. IR: 2935, 2231, 1620, 1447, 1211, 1061, 807 cm^{-1}. Analysis calculated for $C_{25}H_{28}N_4$: C, 76.63; H, 7.83; N, 15.54. Found: C, 76.52; H, 7.95; N, 15.37. An X-ray single-crystal structure was obtained on both compounds **13a** and **13b**, and both appear in the Supporting Information.[19]

4-Cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic Acid Ethyl Ester (8a + 8b). Into a solution of 1-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexane-1,4-dicarbonitrile (**13a** + **13b**) (2.58 g, 7.16 mmol) in EtOH (35 mL) was bubbled dry HCl gas for 20 min. The reaction mixture was stirred 20 min, after which it was concentrated. To the crude product was added toluene (20 mL) and H_2O (20 mL) and the mixture was stirred for 8 h. The layers were separated, and the toluene layer was

concentrated to a crude foam. The diastereoisomeric mixture was isolated by purification by chromatography on silica gel eluting with 4:1 hexanes/ethyl acetate (2.37 g product isolated, 81% yield) and had identical spectroscopic properties of the diastereomeric mixture of the compound prepared from the previous route.

Acknowledgment

We thank Jon Bordner and Debra DeCosta of Pfizer Global Research and Development for the determination of the single-crystal X-ray structure of compounds **5a**, **13a** and **13b** and Raymond Bemish for his help in the identification of impurities using mass spectrometry. We also thank Shane Eisenbeis, Alex Grodski, Rich Buzon and Cliff Meltz for several helpful discussions with regards to the scale-up of this chemistry.

Supporting Information Available

X-ray crystallographic data for compounds **5a**, **13a** and **13b**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review July 30, 2001.

OP010223P