Organic Process Research & Development **2010**, *14*, 1182–1187

A Practical Synthesis of the PDE4 Inhibitor, KW-4490

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Abstract:

A practical and scalable synthesis of a PDE4 inhibitor KW-4490 (1) was developed. This improved synthesis features the construction of the 1-arylcyclohexene (9) by the Diels−Alder reaction followed by a newly established Brønsted acid-promoted hydrocyanation. Subsequent crystallization-induced dynamic resolution enabled the high-yield production of the desired *cis*-isomer (cis-8). The synthesis was achieved in seven steps in 37% overall yield.

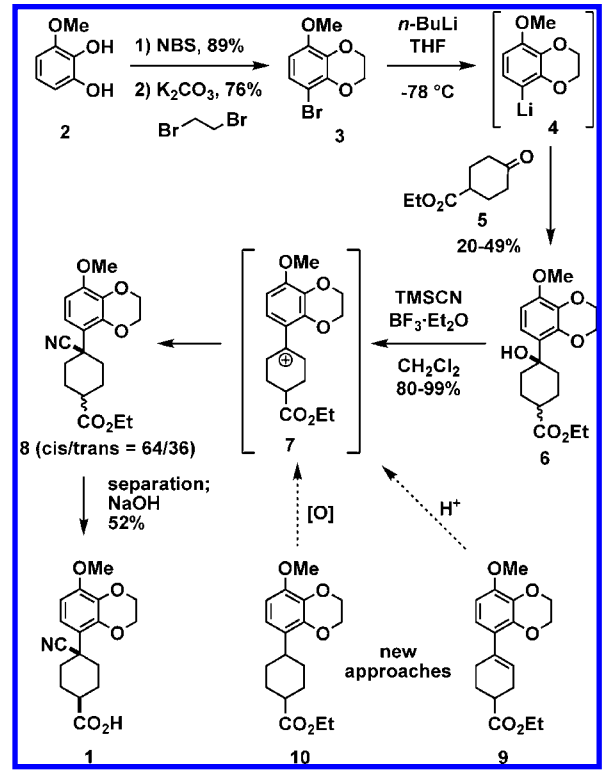
Introduction

Phosphodiesterase 4 (PDE4) is a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase which is located predominantly in inflammatory cells. High levels of cAMP inhibit the production of cytokines and other molecules that modulate the inflammatory response.[1] Therefore, PDE4 inhibitors have emerged as potential therapeutic agents in the treatment of asthma and chronic obstructive pulmonary disease (COPD).[2] Since *cis*-4-cyano-4-(2,3-dihydro-8-methoxy-1,4-benzodioxin-5-yl)cyclohexanecarboxylic acid (KW-4490, **1**) was identified in Kyowa Hakko Kirin as a potent PDE4 inhibitor,[3] multikilogram quantities were thus required in order to carry out both pharmacological profiling and clinical trials. Structurally, the compound presents the interesting synthetic challenges of constructing a tetra-substituted electron-rich benzene, a tertiary benzylic nitrile, and *cis* stereochemistry of a carboxylic acid on a 1,4-disubstituted cyclohexane.

In general, tertiary benzylic nitriles has been prepared by the double alkylation of benzylic nitrile,[4] arylations of secondary nitrile anions with aryl halides,[5] or the displacement of tertiary benzylic alcohol with cyanide.[6] The latest approach was applied to our medicinal chemistry synthesis of **1**, which was suitable for the delivery of multigram quantities (Scheme 1).[3b] However, the synthesis was not directly amenable to large-scale production. The most problematic step is the addition of aryllithium **4** to ketone **5**, because of its low yield and poor reproducibility. Our deuterium oxide quenching experiments suggested that the deprotonation of active protons on **5** was a significantly competing side reaction, which caused both a low yield and complex self-condensed byproducts. Furthermore, the resulting alcohol **6** was a mixture of *cis*/*trans* diastereomers which did not form crystals, but an oily mixture. This finding thereby ruled out the option of purifying **6** by crystallization. Therefore, column chromatography purification was unavoidable to obtain a sufficient quality of the product usable for the following reaction. We were forced to develop a practical, robust, and scalable synthesis for the preparation of **1** while keeping out the alcohol **6**.

Concerning other aspects of the medicinal chemistry synthesis, a cyanide substitution of the alcohol **6** was a high-yield

Scheme 1. **Medical chemistry route**



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Published on Web 07/08/2010

10.1021/op1001287

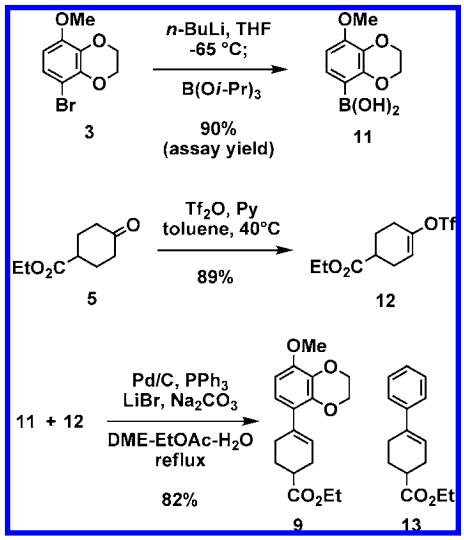
and robust reaction. On the basis of the notion that the intermediate cation **7** should be stabilized by the oxygen substituents, we envisioned that 1-arylcyclohexene (**9**) might be a new precursor for nitrile **8** through protonation (Scheme 1), even though the hydrocyanation of such highly substituted olefins has been very limited.[7] Additionally, we planned an alternative approach via the oxidative cyanation of 1-arylcyclohexane (**10**), in which case cation **7** also emerges as an intermediate.[8]

In the current article, we report our approaches for the synthesis of **1** featuring the scalable construction of arylcyclohexene **9**, trials for the introduction of the cyano group at the benzylic position, which resulted in the discovery of Brønsted acid-promoted hydrocyanation,[9] and the crystallization-induced dynamic resolution of the resulted nitrile **8** diastereomers.

Results and Discussion

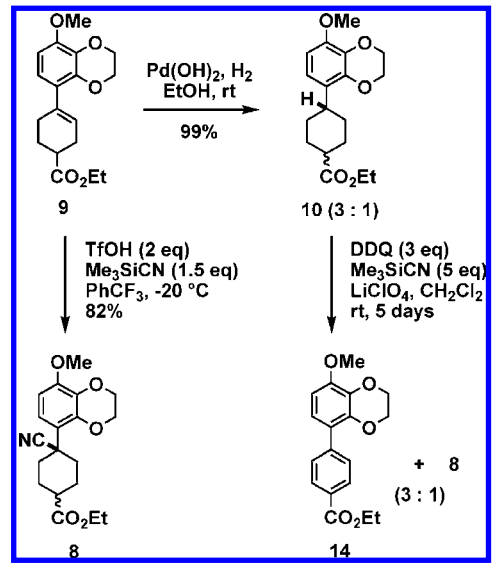
Our study began with the preparation of 1-arylcyclohexene (**9**) by Suzuki−Miyaura cross-coupling (Scheme 2). Both boronic acid **11** and enol triflate **12** were prepared from the above medicinal chemistry intermediates **3** and **5**, respectively. Using triisopropyl borate as a boron source,[10] the assay yield of the boronic acid was approximately 90%, but we were unable to isolate **11** by crystallization due to the contamination by impurities. Therefore, we used an extracted solution of the boronic acid for the Suzuki−Miyaura coupling. Notably, the electron-rich boronic acid was gradually decomposed via protodeboronation[11] in the presence of a trace of acid, and therefore the extract was stocked after neutralization by aqueous sodium hydroxide.

Scheme 2. **Suzuki−Miyaura coupling route**



The preparation of the enol triflate **12** was achieved by applying a 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)-free condition as established in our laboratories. DTBMP is the commonly used effective non-nucleophilic base for enol triflate synthesis,[12] and we first employed this method. However, in view of its high cost and low availability in large quantities, we substituted a simpler method using pyridine instead of DTBMP in the toluene solvent.[13] It was essential to use a slight excess of triflic anhydride over pyridine to achieve a good conversion, affording a 89% yield of triflate **12** after a SiO_2 batch treatment. This newly established enol triflate synthesis will be reported elsewhere.

Scheme 3. **Cyano group introduction**



A study of the Suzuki−Miyaura cross coupling between **11** and **12** identified the optimal reaction conditions as a 1:9 molar ratio of palladium on carbon (Pd/C) and PPh_3 in refluxing DME−H_2O with K_2CO_3. The optimal ratio of palladium and phosphine minimized byproduct **13** arising from an aryl−aryl exchange, which might be enhanced by electron-donating substituents between the palladium center and the phosphine ligand.[14] The assay yield of **9** was 93% according to an HPLC analysis, and as expected, **9** was easily crystallized with a yield of 82%. This synthesis was convenient for procuring small amounts of **9** in the early stages of our study. However, there were still several issues in the large-scale preparation of both **11** and **12**, especially the SiO_2 batch treatment of triflate **12** and the low temperature below −65 °C for the lithiation of **3**.

Facing the key issue of cyano group introduction, we first examined DDQ-mediated oxidative benzylic cyanation (Scheme 3).[8] The hydrogenation of **9** afforded cyclohexane **10** as a 3/1 *cis*/*trans* mixture. The mixture was subjected to DDQ and trimethylsilyl cyanide in dichloromethane at room temperature.

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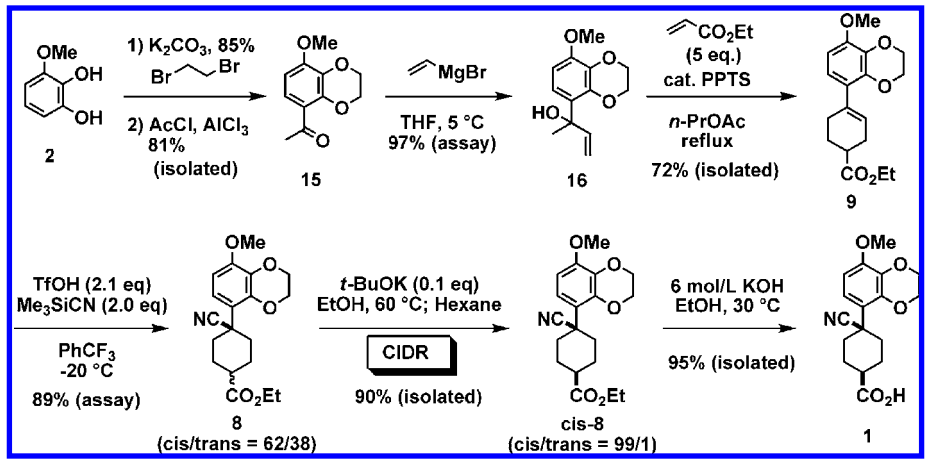
Scheme 4. **Process route via Diels−Alder and CIDR**

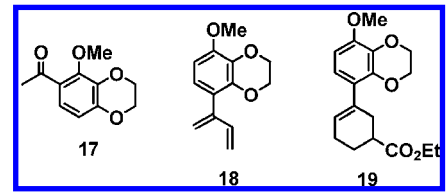


The reaction was slow and resulted in the formation of biphenyl **14** as the main product, while the desired nitrile was the minor product. This is most likely due to the tendency of proton-loss from the benzylic cation **7**, and subsequent oxidation afforded the aromatized product.

Therefore, we next examined the more direct approach via hydrocyanation of cyclohexene **9**. As reported previously, we have examined various Brønsted acids. Triflic acid was found to be the most effective in promoting the desired hydrocyanation under mild conditions. Trimethylsilyl cyanide was optimal as a cyanide source, and a slight excess acid equivalent was required for promoting this reaction.[9] Successful completion of this reaction facilitated compound **1** synthesis, avoiding issues around alcohol **6**, and shifted our focus into the development of a more practical synthesis of **9**.

Through a retrosynthesis analysis of **9**, we were attracted by an approach featuring the Diels−Alder reaction to construct the cyclohexene ring. We expected that the electron-donating nature of the benzene ring should be advantageous in terms of the reactivity and selectivity of the Diels−Alder reaction.

The optimized process route is shown in Scheme 4. Catechol **2** was treated with 1,2-dibromoethane followed by selective Friedel−Crafts acetylation to give the methylketone **15**. The observed regioisomer **17** was only 1%. This high selectivity can be explained by steric repulsion between the methyl group and acylating reagent. Because the normal addition of vinyl Grignard into a solution of **15** produced a considerable amount of a self-aldol adduct, the optimal method was thus determined to be the inverse addition of **15** into a vinylmagnesium bromide solution at 5 °C, thereby giving tertiary alcohol **16** with a 97% assay yield. Due to difficulty in crystallization, alcohol **16** was used without purification. Dehydration proceeded smoothly at 80 °C in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate. Subsequent Diels−Alder reaction required a relatively low temperature (only 100 °C) to allow for completion within a reasonable time period of several hours with ethyl acrylate to give the desired adduct **9** with ∼5/1 regioselectivity. However, the diene **18** was unstable during both evaporation and storage. Therefore, we examined a one-pot procedure which was successfully achieved by refluxing the crude **16** in propyl acetate in the presence of ethyl acrylate and pyridinium *p*-toluenesulfonate to afford **9** in a 77% assay yield. In order to eliminate the generating water using the Dean−Stark trap for the completion of the one-pot reaction, propyl acetate was found to be optimal because its boiling point (101 °C) is close to that of both water and ethyl acrylate (100 °C). Although 15% of regioisomer **19** was obtained in the reaction, it was effectively removed during crystallization from ethanol/water to afford pure **9** in the 72% isolated yield. This route appears to be superior to the previous Suzuki−Miyaura coupling route from the viewpoint of scale-up, because there are no low-temperature reactions or column chromatography steps.



The optimal conditions for the hydrocyanation were identified as using 2.1 equiv of triflic acid and 2.0 equiv of trimethylsilyl cyanide in trifluorotoluene at −20 °C. Arylalkene **9** was successfully converted to the tertiary nitrile **8** with an 89% assay yield in an approximately 62:38 *cis*/*trans* mixture. This poor *cis*/*trans* selectivity remained among various conditions including varying temperature, solvents, and CN sources.[9] Therefore, the development of a recovery method via isomerization of **trans-8** was strongly required. Base-induced isomerization was amenable by treatment with a base such as potassium *tert*-butoxide, but was stopped at a 75/25 *cis*/*trans* ratio. Isomerization from both pure **cis-8** and pure **trans-8** gave the same result, which proved that the thermodynamic equilibrium point is unfortunately 75/25. An observation that **cis-8** was less soluble than **trans-8** in ethanol led us to speculate that crystallization-induced dynamic resolution (CIDR)[15] could be applied to solve this problem. In the presence of a catalytic amount of potassium *tert*-butoxide, the ethanol suspension of crude **8** (*cis*/*trans* = 62/38) was stirred with simultaneous heating, and then the poor solvent hexane was added portionwise in order to push **cis-8** to precipitate. Continuous isomerization in the solution state and simultaneous preferential crystallization of **cis-8** successfully increased the ratio to 99/1 with a 90% isolated yield. The last step, the basic hydrolysis of **cis-8**, proceeded smoothly at a moderate temperature without

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any isomerization. For the final recrystallization, the use of alcoholic solvents was eliminated because of the contamination of a small amount of the corresponding ester. The recrystallization was performed with acetone−water to give compound **1** in a 95% yield and a 99.9% purity.

Conclusions

In summary, the successful short and practical synthesis of PDE4 inhibitor KW-4490 (**1**) was developed. The synthesis was achieved in seven steps and with a 37% overall yield, of which four steps were carbon−carbon bond-forming reactions using simple synthons. The key to the success of this new method was the development of a novel hydrocyanation reaction of cyclohexene **9**, which was constructed by a one-pot dehydration Diels−Alder sequence. Subsequent successful crystallization-induced dynamic resolution of **cis-8** enhanced the practicability of the synthesis. Multikilogram quantities of KW-4490 (**1**) have now been produced in our laboratories. We believe that this synthesis highlights the benefits of a problem-driven approach toward the development of new synthetic methodologies.

Experimental Section

General Information. All reagents and solvents are commercially available (Tokyo Kasei Kogyo Co., Ltd.; Sigma-Aldrich Co.) and used without further purification. ^{1}H NMR spectra were obtained on a JEOL JNM-LA300 spectrometer (300 MHz) or Bruker AVANCE 500 spectrometer (500 MHz). Chemical shifts (δ) are reported in ppm. Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), brs (broad singlet). Proton-decoupled ^{13}C NMR spectra were obtained on a JEOL JNM-LA300 spectrometer (75 MHz) or Bruker AVANCE 500 spectrometer (125 MHz). IR frequencies are given in cm^{-1}, and spectra were obtained on a Shimadzu FT-IR8700 spectrometer. Mass spectra and high-resolution mass spectra were obtained on a Micromass LCT spectrometer. HPLC analyses were performed on a Hitachi L-4000 system. GC analyses were performed on a Shimadzu GC-14A equipped with a capillary column TC-5. Melting points (mp) were determined on a Mettler FP61.

Ethyl 4-Trifluoromethylsulfonyloxy-3-cyclohexenecarboxylate (12). To a solution of pyridine (10.4 mL, 12.9 mmol, 1.10 equiv) in toluene (350 mL) was added dropwise Tf_2O (21.8 mL, 13.0 mmol, 1.11 equiv) over 30 min at 15 °C under N_2. Ketone **5** (20.0 g, 11.8 mmol) was added to the mixture with toluene (10 mL) at room temperature. The mixture was heated at 40 °C. Tf_2O was added after 10 h (0.10 mL, 0.058 mmol, 0.005 equiv) and 12 h (0.10 mL, 0.058 mmol, 0.005 equiv). After heating at 40 °C for additional 2 h, the reaction mixture was assayed by GC to contain **12** (91%). Water (200 mL) was added at 15 °C to the reaction mixture. After separation, SiO_2 (60 g) was added to the organic layer and then filtered and washed with toluene (20 mL). The filtrate was evaporated to give **12** (31.6 g, 89%); ^{1}H NMR ($CDCl_3$) δ 5.79−5.77 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.64−2.53 (m, 1H), 2.48−2.38 (m, 4H), 2.18−2.09 (m, 1H), 1.99−1.86 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.0, 148.5, 118.6 (q, J = 319.6 Hz), 116.9, 60.9, 37.9, 26.6, 26.1, 25.1, 14.1; IR (film) 2984, 2941, 1732, 1695, 1418, 1248, 1209, 1142, 1057, 1036, 876 cm^{-1}; LC/MS ESI(+) m/z 303 $[M + H]^+$.

Ethyl 4-(2,3-Dihydro-8-methoxy-1,4-benzodioxin-5-yl)-3-cyclohexenecarboxylate (9): Suzuki−Miyaura coupling. Under N_2, a solution of boronic acid **11**[9] (8.39 g, 40.0 mmol, 126 mL of DME/ethyl acetate solution), triflate **12** (14.5 g, 1.2 equiv), 5% Pd/C (1.98 g, 0.01 equiv), PPh_3 (943 mg, 0.09 equiv), and K_2CO_3 (11.0 g, 2.0 equiv) in DME/water (46 mL: 84 mL) was heated under reflux for 3 h and then filtered through pad of Celite. The filtrate was separated, and the aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layers were washed with water (100 mL), concentrated under reduced pressure, and recrystallized from ethanol/water (7:3 v/v, 42 mL) to afford **9** (10.4 g, 32.7 mmol, 82%) as a white solid: mp 88 °C; ^{1}H NMR ($CDCl_3$) δ 6.65 (d, J = 8.5 Hz, 1H), 6.44 (d, J = 8.5 Hz, 1H), 5.80−5.75 (m, 1H), 4.32−4.24 (m, 4H), 4.16 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 2.50−2.41 (m, 1H), 2.31−2.19 (m, 4H), 2.01−1.90 (m, 1H), 1.67−1.54 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.5, 147.7, 141.2, 135.1, 132.9, 124.9, 123.7, 119.1, 103.3, 64.2, 64.0, 60.2, 56.0, 39.1, 28.2, 28.0, 25.7, 14.2; IR (KBr) 2932, 1720, 1607, 1502, 1458, 1373, 1286, 1169, 1115 cm^{-1}; HRMS ESI(+) calcd for $C_{18}H_{23}O_5$ $[M + H]^+$ 319.1545, found 319.1540.

Hydrogenation and Oxidative Cyanation of 9. A solution of cyclohexene **9** (32.0 mg, 0.10 mmol) and 20% $Pd(OH)_2$/C (6 mg, 10 wt %) in ethanol/ethyl acetate (5 mL:5 mL) was stirred under H_2 (1 atm) at room temperature for 2 h. The reaction mixture was filtered and concentrated to obtain cyclohexane **10** (3:1 diastereomer mixture: 31.8 mg, 0.10 mmol, 99%) as a colorless oil. The crude cyclohexane **10** (6.4 mg, 0.02 mmol) was dissolved in CH_2Cl_2 (1 mL), and $LiClO_4$ (0.4 mg, 0.004 mmol, 0.2 equiv), Me_3SiCN (0.0063 mL, 0.05 mmol, 2.5 equiv), and DDQ (6.8 mg, 0.03 mmol, 1.5 equiv) were added. The mixture was stirred at room temperature for 4 h, and then Me_3SiCN (6.3 μL, 0.05 mmol, 2.5 equiv), $LiClO_4$ (10 mg, 0.09 mmol, 4.7 equiv), and DDQ (5.8 mg, 0.03 mmol, 1.3 equiv) were added, and the mixture was stirred for 66 h at room temperature. The resultant mixture was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and evaporated. ^{1}H NMR spectrum of the residue indicated that the ratio of biphenyl compound **14**, **cis-8**, and **trans-8** was 6:1:1. An analytical sample of **14** was obtained by SiO_2 column chromatography (hexane/ethyl acetate; 3:1); ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.5 Hz, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.43−4.27 (m, 4H), 4.12 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.6, 149.0, 142.4, 141.4, 133.4, 129.3, 129.2, 128.6, 122.7, 121.4, 104.0, 64.3, 64.2, 60.8, 56.1, 14.4; IR (KBr) 2985, 1794, 1604, 1366, 1270, 1017, 772 cm^{-1}; HRMS ESI(+) calcd for $C_{18}H_{19}O_5$ $[M + H]^+$ 315.1232, found 315.1235.

2,3-Dihydro-5-methoxy-1,4-benzodioxin. Under N_2 atmosphere, a solution of 3-methoxycatechol **2** (25.3 g, 180 mmol), K_2CO_3 (104.5 g, 756 mmol, 4.2 equiv), and 1,2-dibromoethane (74.4 g, 396 mmol, 2.2 equiv) in DMF (100 mL) was heated at 60 °C for 6 h. The mixture was quenched with water and then extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to afford the title compound (25.4 g, 153 mmol, 85%) as an amber oil; ^{1}H NMR ($CDCl_3$) δ 6.77 (dd, J = 8.4,

8.1 Hz, 1H), 6.54 (d, J = 8.4, 1.5 Hz, 1H), 6.49 (d, J = 8.1, 1.5 Hz, 1H), 4.34−4.24 (m, 4H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.1, 144.2, 133.3, 120.2, 110.1, 104.1, 64.5, 64.2, 56.1; IR (film) 2936, 2876, 1595, 1497, 1477, 1331, 1285, 1238, 1211, 1113, 1051, 952, 885, 768, 718 cm^{-1}; LC/MS ESI(+) m/z 167 $[M + H]^+$.

5-Acetyl-2,3-dihydro-8-methoxy-1,4-benzodioxin (15). [16] Under N_2 atmosphere, to a solution of $AlCl_3$ (12.0 g, 90 mmol, 1.5 equiv) in nitromethane (200 mL) was added acetyl chloride (5.57 mL, 78 mmol, 1.3 equiv) at 0 °C. Then a solution of 2,3-dihydro-5-methoxy-1,4-benzodioxin (10.0 g, 60 mmol) in CH_3NO_2 (100 mL) was added dropwise over 40 min. After stirring at the same temperature for 3 h, 1 mol/L HCl was added. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$ and concentrated. The residue was dissolved in isopropyl alcohol (25 mL) at 70 °C, cooled to room temperature, and stirred at 0 °C for 3 h. The precipitate was filtered to afford **15** (10.1 g, 49 mmol, 81%) as a pale-yellow solid: mp 81 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 8.9 Hz, 1H), 6.54 (d, J = 8.9 Hz, 1H), 4.39−4.32 (m, 4H), 3.91 (s, 3H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.1, 152.4, 144.6, 132.9, 122.7, 121.3, 103.5, 64.2, 63.9, 56.2, 31.5; IR (KBr) 2982, 1676, 1597, 1501, 1468, 1441, 1373, 1356, 1281, 1207, 1178, 1136, 1113, 1069, 1042, 976, 935, 800, 746, 677, 633, 594, 546 cm^{-1}; LC/MS ESI(+) m/z 209 $[M + H]^+$. The analytical sample of **17** was obtained by SiO_2 column chromatography (hexane/ethyl acetate; 5/2): ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 4.33−4.26 (m, 4H), 3.94 (s, 3H), 2.60 (s, 3H); LC/MS ESI(+) m/z 209 $[M + H]^+$.

3-(2,3-Dihydro-8-methoxy-1,4-benzodioxin-5-yl)-1-buten-3-ol (16). To a stirred solution of vinylmagnesium bromide (288 mL, 0.80 mol/L solution in THF, 231 mmol, 1.6 equiv) in THF (240 mL), was added dropwise a solution of ketone **15** (30.0 g, 144 mmol) in THF (120 mL) over 30 min at 5 °C under N_2 atmosphere. The reaction mixture was stirred at the same temperature for 45 min and then quenched with a saturated aqueous NH_4Cl (300 mL), diluted with saturated aqueous NaCl (100 mL), and extracted with ethyl acetate (300 mL). The extract was washed with saturated aqueous NaCl (200 mL), dried over Na_2SO_4 (50 g), and concentrated to afford crude **16** (HPLC assay 139 mmol; net 32.9 g, 97% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.83 (d, J = 8.7 Hz, 1H), 6.47 (d, J = 8.7 Hz, 1H), 6.18 (dd, J = 17.2, 10.6 Hz, 1H), 5.11 (dd, J = 17.2, 1.1 Hz, 1H), 5.04 (dd, J = 10.6, 1.1 Hz, 1H), 4.36−4.24 (m, 4H), 3.87 (s, 3H), 1.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.4, 144.8, 141.7, 133.4, 126.9, 117.2, 111.6, 103.3, 74.6, 64.1, 64.0, 56.0, 27.4; IR (film) 3541, 3086, 2978, 2978, 1609, 1504, 1443, 1373, 1281, 1115, 999, 953, 891, 829, 733 cm^{-1}; HRMS ESI(−) calcd for $C_{13}H_{15}O_4$ $[M - H]^-$ 235.0970, found 235.0966.

2-(2,3-Dihydro-8-methoxy-1,4-benzodioxin-5-yl)-1,3-butadiene (18). Under N_2 atmosphere, a solution of alcohol **16** (0.47 g, 2.0 mmol) and pyridinium *p*-toluenesulfonate (2.5 mg, 0.01 mmol, 0.005 equiv) in toluene (100 mL) was heated at 80 °C for 2 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and evaporated to give diene **18** as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.65 (d, J = 8.4 Hz, 1H), 6.58 (dd, J = 17.2, 6.7 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 5.40−5.39 (m, 1H), 5.16−5.14 (m, 1H), 5.12 (d, J = 6.7 Hz, 1H), 4.93 (d, J = 17.2 Hz, 1H), 4.33−4.22 (m, 4H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.4, 144.8, 141.4, 138.1, 132.9, 121.6, 121.3, 118.6, 116.2, 103.5, 64.3, 64.2, 56.0; IR (film) 3086, 2970, 2931, 1609, 1504, 1443, 1373, 1323, 1277, 1211, 1115, 1076, 1053, 953, 891, 799, 760 cm^{-1}; LC/MS ESI(+) m/z 219 $[M + H]^+$.

Ethyl 4-(2,3-Dihydro-8-methoxy-1,4-benzodioxin-5-yl)-3-cyclohexenecarboxylate (9) and Isomer (19): Diels−Alder Reaction. Under N_2 atmosphere, a solution of the above crude **16** (net 22.7 g, 96 mmol), ethyl acrylate (52 mL, 480 mmol, 5 equiv), and pyridinium *p*-toluenesulfonate (145 mg, 0.58 mmol, 0.006 equiv) in *n*-PrOAc (114 mL) was heated under reflux. H_2O (~1.7 mL) was eliminated from the refluxing reaction mixture using Dean−Stark water separator. After 8 h, the reaction mixture was cooled, washed with a combined solution of saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was concentrated to afford a crude mixture of cyclohexene **9** and isomer **19** (combined HPLC assay yield 92.1%; ratio =5.3:1). The residue was dissolved in ethanol (58 mL) and H_2O (10 mL) at 70 °C and cooled to 3 °C. The formed precipitates were collected by filtration to obtain **9** (22.0 g, 69 mol, 71.8% yield) as a pale-yellow solid. Analytical sample of isomer **19** was obtained from concentrated residue of the above filtrate through SiO_2 column chromatography (hexane/ethyl acetate, 10:1 → 3:1); ^{1}H NMR ($CDCl_3$) δ 6.65 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 5.77 (brs, 1H), 4.36−4.26 (m, 4H), 4.15 (q, J = 7.2 Hz, 2H) 3.86 (s, 3H), 2.72−2.53 (m, 3H), 2.31−2.22 (m, 2H), 2.10−2.00 (m, 1H), 1.81−1.67 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.9, 148.0, 141.4, 134.5, 132.9, 125.8, 125.4, 119.9, 103.4, 64.2, 64.1, 60.2, 56.0, 40.0, 31.2, 25.1, 24.8, 14.2; IR (film) 2932, 1728, 1605, 1504, 1443, 1377, 1284, 1173, 1115, 1034, 953, 891 cm^{-1}; HRMS ESI(+) calcd for $C_{18}H_{23}O_5$ $[M + H]^+$ 319.1545, found 319.1557.

Ethyl 4-Cyano-4-(2,3-dihydro-8-methoxy-1,4-benzodioxin-5-yl)cyclohexanecarboxylate (8). *Caution!* When CF_3SO_3H and Me_3SiCN are mixed, in situ HCN formation occurs. Be sure to seal the reaction flask until basic quench, and keep handling under a well-ventilated fume hood. Prepare the CN testing tube for leak check. To a solution of CF_3SO_3H (126.3 g, 841 mmol, 2.1 equiv) and Me_3SiCN (79.5 g, 801 mmol, 2.0 equiv) in $PhCF_3$ (383 mL) was added dropwise a solution of cyclohexene **9** (127.5 g, 400 mmol) in $PhCF_3$ (892 mL) over 60 min at −20 °C under N_2 atmosphere. The reaction mixture was allowed to warm to −2 °C over 4 h and quenched with 1.5 mol/L aqueous NaOH (1250 mL). After stirring for 30 min, the organic layer was separated, washed with 1.5 mol/L aqueous NaOH (1250 mL) and 1.0 mol/L aqueous NaCl (1000 mL × 2), and dried over $MgSO_4$(50 g), then concentrated to give a *cis*/*trans* mixture of nitrile **8** (HPLC assay; *cis*/*trans* = 62/38, 355 mmol, net 122.6 g, 88.7% yield). The analytical sample of **trans-8** was obtained by SiO_2 column chromatography (hexane/ethyl acetate, 3:1): mp 104 °C; ^{1}H NMR ($CDCl_3$) δ 6.82 (d, J

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= 8.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.36−4.33 (m, 4H), 4.15 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 2.75 (brs, 1H), 2.42−1.99 (m, 8H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 148.8, 142.2, 133.5, 122.1, 121.0, 116.9, 103.2, 64.2, 63.6, 60.3, 55.9, 39.7, 38.0, 31.0, 24.2, 14.2; IR (KBr) 2970, 2941, 2228, 1717, 1609, 1506, 1464, 1377, 1329, 1286, 1123, 1040, 953, 891, 793 cm^{-1}; HRMS ESI(+) calcd for $C_{19}H_{24}NO_5$ $[M + H]^+$ 346.1654, found 346.1631.

Crystallization-Induced Dynamic Resolution of cis-8. To a suspension of the *cis*/*trans* mixture **8** (net 28.5 g, 82.5 mmol, *cis*/*trans* = 61/39) in anhydrous ethanol (15 mL) and hexane (60 mL), was added *t*-BuOK (0.93 g, 8.26 mmol, 0.1 equiv) and heated under reflux. After 3 h, hexane (75 mL) was added portionwise and the refluxing was continued for 1 h. The resulting suspension was cooled to 20 °C over 1 h, stirred for 1 h at the same temperature, and filtered to afford crude **cis-8** (27.5 g, *cis*/*trans* = 99.6/0.4) as pale-yellow crystals. The crude **cis-8** was dissolved in ethanol (82.5 mL) at 65 °C. The solution was cooled to 5 °C over 1 h and stirred for 1 h at the same temperature. The formed precipitates were collected by filtration to provide **cis-8** (25.8 g, *cis*/*trans* = 99.97/0.03, 74.7 mmol, 90.4% yield) as a white solid: mp 131 °C; ^{1}H NMR ($CDCl_3$) δ 6.84 (d, J = 8.9 Hz, 1H), 6.49 (d, J = 8.9 Hz, 1H), 4.39−4.33 (m, 4H), 4.17 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 2.44 (brd, J = 12.6 Hz, 2H), 2.32 (tt, J = 11.8, 3.8 Hz, 1H), 2.18−1.95 (m, 4H), 1.86 (dt, J = 3.6, 12.6 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.5, 148.9, 142.2, 133.7, 121.7, 121.0, 116.8, 103.3, 64.2, 63.7, 60.5, 56.0, 42.3, 40.0, 33.6, 25.8, 14.2; IR (KBr) 2953, 2228, 1722, 1607, 1504, 1460, 1381, 1325, 1281, 1117, 1043, 953, 787 cm^{-1}; HRMS ESI(+) calcd for $C_{19}H_{24}NO_5$ $[M + H]^+$ 346.1654, found 346.1675.

cis-4-Cyano-4-(2,3-dihydro-8-methoxy-1,4-benzodioxin-5-yl)cyclohexanecarboxylic Acid (1). A mixture of ester **cis-8** (20.0 g, 57.9 mmol), ethanol (100 mL), and 6 mol/L KOH (19 mL) was stirred at room temperature for 4 h. The resultant mixture was diluted with water (102 mL), cooled to 5 °C, and neutralized with 6 mol/L HCl. The precipitate was collected by filtration and dried to give crude carboxylic acid **1** (18.2 g, 57.4 mmol). The crude **1** (18.0 g, 56.7 mmol) was dissolved in acetone (170 mL) and water (30 mL) under reflux. The solution was filtered hot and maintaining 55 °C during addition of water (180 mL) to form precipitation. The suspension was cooled to 5 °C, stirred 3 h, and filtered to obtain **1** (17.2 g, *cis*/*trans* = >99.99/<0.01, 54.2 mmol, 95% yield) as a white solid: mp 245 °C; ^{1}H NMR (DMSO-d_6) δ 12.24 (s, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 4.33−4.23 (m, 4H), 3.75 (s, 3H), 2.36−2.25 (m, 3H), 2.06−1.98 (m, 2H), 1.86−1.64 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 175.9, 148.6, 141.9, 133.5, 121.6, 120.5, 116.3, 103.9, 63.7, 63.4, 55.4, 41.0, 38.9, 32.9, 25.6; IR (KBr) 3288, 2930, 2232, 1730, 1508, 1456, 804 cm^{-1}; HRMS ESI(−) calcd for $C_{17}H_{18}NO_5$ $[M - H]^-$ 316.1185, found 316.1195.

Acknowledgment

We thank Drs. Masaji Kasai, Masashi Yanase, and Yoshiaki Masuda for helpful discussions, and Hikaru Nishimura for HRMS analysis at former Sakai Research Laboratories of Kyowa Hakko Kogyo.

Supporting Information Available

Copies of ^{1}H and ^{13}C NMR spectra for compounds **14**, **16**, **18**, and **19**. HPLC and GC methods. This material is available free of charge via the Internet at http://pubs.acs.org/.

Received for review May 10, 2010.

OP1001287