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Practical and Scalable Synthesis of a Selective CCK_1 Receptor Antagonist

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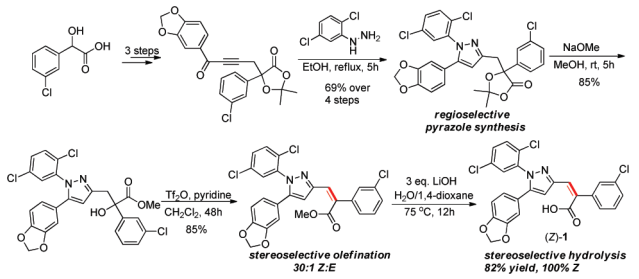
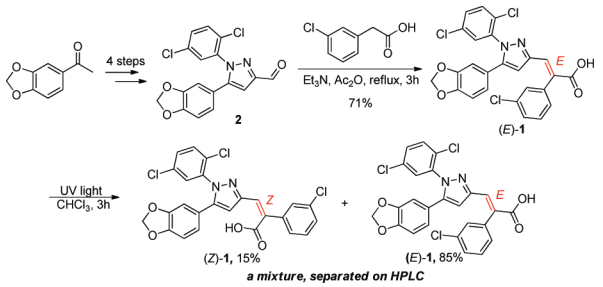


We describe a practical and scalable route to compound (*Z*)-**1**, a selective CCK_1 receptor antagonist. Notable features of this concise route are (1) a regioselective construction of the pyrazole core through the reaction of an aryl hydrazine and an elaborated acetylenic ketone, (2) a Tf_2O/pyridine mediated *Z*-selective dehydration of an α-hydroxyester, and (3) a stereoselective hydrolysis. The sequence is high-yielding and amenable for large-scale synthesis.

Cholecystokinin (CCK) was first identified from extracts of porcine intestinal mucosa in 1966. A 33 amino acid peptide hormone, CCK regulates a variety of physiological processes in response to food intake.[1] These processes include gall bladder contraction, pancreatic enzyme secretion, gastric acid secretion, gastric emptying, and duodenal/colonic motility. In addition, CCK is abundantly found in the CNS and is thought to be involved in aspects of nociception, satiety, anxiogenesis, memory, and learning.[2]

The biological actions of CCK are mediated through two G-protein coupled receptors, CCK_1 (formerly CCK-A) and CCK_2 (formerly gastrin/CCK-B). The actions of CCK on gall bladder contraction, pancreatic enzyme secretion, duodenal motility, and gastric emptying rate are believed to be regulated through agonism of the CCK_1 receptor. Therefore, a number of CCK_1 antagonists have been evaluated in the clinic for potential application in irritable bowel syndrome (IBS), nonulcer dyspepsia, biliary colic, chronic constipation, and pancreatic cancer.[3,2a] Our laboratories have also disclosed a series of selective, nonpeptide CCK_1 antagonists.[4] Recent efforts in this area identified compound (*Z*)-**1** (Scheme 1) as a molecule of interest for the continued study of CCK_1 antagonism and its applications within the mammalian system.

SCHEME 1. The Initial Synthesis of Compound (*Z*)-1



The original synthesis of compound (*Z*)-**1** involves a six-step sequence.[5] The most challenging step of the synthesis was the construction of the trisubstituted *Z* olefin. Perkin condensation[6] of aldehyde **2** with 3-chlorophenyl acetic acid afforded exclusively the thermodynamically more stable (*E*)-**1**. Photoisomerization followed by HPLC separation was required to produce the desired (*Z*)-**1** in low yield. An alternative stereoselective route was recently reported featuring a sequential functionalization of a geminal dibromo vinyl precursor.[7] However, the extreme cryogenic conditions (−116 °C) and the low yield precluded its use for the further up scaling. Herein, we report efforts that culminated in a practical and scalable synthesis of compound (*Z*)-**1**.

We recognized that the key issue to address for the synthesis of (*Z*)-**1** was installation of the *Z* configured trisubstituted olefin. Stereoselective synthesis of thermodynamically disfavored *Z*-α,β-unsaturated acid derivatives is a classic problem in organic synthesis. Careful examination of the available olefination methods in the literature indicated that the Horner−Wadsworth−Emmons (HWE)

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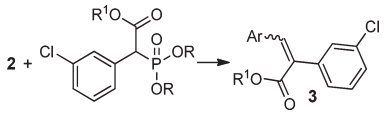
TABLE 1. The HWE Reaction with Different Phosphonates[a]



entry	R^1	R	*Z*/*E* ratio	yield, %
1	Et	Et	3:7	90
2	Et	CF_3CH_2	4:1	84
3	Me	CF_3CH_2	3:1	95
4	Me	Ph	4:1	50

[a]Conditions: 1.2 equiv of $KOBu^t$, 3 equiv of 18-crown-6, THF, 0 °C−rt.

reaction appeared most promising for stereoselective *Z*-olefination. With easily accessible aldehyde **2** in hand, we decided to study the HWE reaction in detail. The classic HWE conditions with diethyl phosphonate favored the formation of the *E* isomer (Table 1, entry 1). Still and Gennari have previously demonstrated that electronically modified HWE reagents can have profound effects on the stereochemical course of these reactions.[8] Specifically, employment of electron-withdrawing bistrifluoroethyl phosphonate reagents was shown to promote *Z*-olefin formation. Indeed, in our case, the Still−Gennari variant of the HWE reagent gave rise to a 4:1 *Z*:*E* mixture (entry 2). We also investigated the effect of changes to R^1; substitution of ethyl with methyl afforded a lower *Z* to *E* ratio but a higher yield (entry 3). The Ando modification of the HWE reaction[9] resulted in comparable *Z* selectivity, but in a lower yield (entry 4). Our attempts to further improve the *Z* selectivity of the Still−Gennari protocol by the use of additives, changes in addition order or time, and solvent switches were largely unsuccessful.

With the 3:1 *Z*:*E* mixture of **3** in hand, we reasoned that a significant rate difference in hydrolysis of the *Z* and *E* olefinic acid esters[10] might provide a facile isolation of the desired *Z* isomer. Indeed, we found that under carefully controlled conditions (room temperature, 2.0 equiv of LiOH, 3:1:1 THF:EtOH:H_2O), the undesired ester (*E*)-**3** was preferentially hydrolyzed to acid (*E*)-**1** whereas the desired ester (*Z*)-**3** remained intact. The polarity difference of acid (*E*)-**1** and ester (*Z*)-**3** made isolation rather easy (Scheme 2).

With pure ester (*Z*)-**3** in hand, the final hydrolysis to compound (*Z*)-**1** was surprisingly difficult because of the thermodynamic instability of the *Z* olefin.[11] Aqueous alkaline hydrolysis under reflux conditions resulted in the complete isomerization of the double bond to (*E*)-**1** (Table 2, entry 1). Different hydroxide counterions (Li^+, Na^+, and K^+) did not significantly impact the outcome (entries 2−4). Changing the solvent systems to MeOH/H_2O (B) or THF/H_2O (C) greatly slowed the hydrolysis reaction probably due to the poor solubility of (*Z*)-**3** (entries 5−7). Increasing the quantity of base to 10 equiv sped up the hydrolysis reaction but also the isomerization process (entry 7). Switching to an alternate solvent system, 1,4-dioxane/H_2O (D) greatly

SCHEME 2. The Stereoselective Hydrolysis

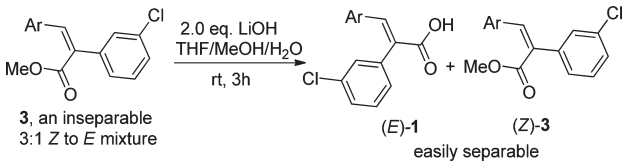
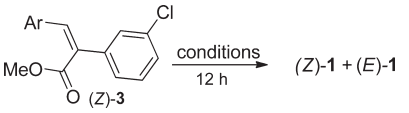


TABLE 2. Hydrolysis of Pure (*Z*)-3



entry	base	equiv	solvents[a]	*T*, °C	(*Z*)-**3**:(*E*)-**1**:(*Z*)-**1**[b]
1	LiOH	5	A	reflux	0:100:0
2	KOH	5	A	50	5:20:75
3	NaOH	5	A	50	35:12:53
4	LiOH	5	A	50	15:21:64
5	LiOH	5	B	50	90:1:9
6	LiOH	5	C	50	90:2:8
7	LiOH	10	C	55	0:95:5
8	LiOH	5	D	55	10:0:90
9	LiOH	5	D	75	0:3:97
10	LiOH	3	D	75	0:3:97

[a]Solvent A: 2-Me-THF/MeOH/H_2O. Solvent B: MeOH/H_2O. Solvent C: THF/H_2O. Solvent D: 1,4-dioxane/H_2O. [b]On the basis of integration of HPLC peaks.

facilitated the hydrolysis process (entry 8). Increasing the temperature to 75 °C drove the reaction to completion but also resulted in ~3% isomerization (entry 9). The amount of base could be reduced to 3.0 equiv to provide an almost identical result (entry 10). Fortunately, the small amount of undesired (*E*)-**1** could be easily excluded by trituration from a mixed solvent of DCM/EtOAc/hexanes. Therefore, the first chromatography-free route for the synthesis of compound (*Z*)-**1** on the multigram scale was developed.

Although the above route provided compound (*Z*)-**1** on a multigram scale, the moderate 3:1 *Z*:*E* selectivity in the key olefination step and the reliance on the noncommercially available Still−Gennari phosphonate negatively affected the overall throughput of this process. We embarked on pursuing a new synthetic strategy to construct the *Z* olefin. Almost all the classic olefination reactions such as the HWE reaction rely on selective dehydration of a β-hydroxyester to set the olefin geometry (Figure 1). This often favors the thermodynamically more stable *E* isomer, as we experienced above and witnessed in many examples in the literature. Recently, we have demonstrated that Tf_2O/pyridine-mediated dehydration of α-hydroxyesters provides a powerful method for stereoselective synthesis of *Z*-α-arylacrylates on simple substrates.[12] Whether this new method could apply to fully elaborated substrate **4** remained to be investigated.

To answer this question, an easy access to precursor **4** was required. Exploiting our previous experience on the synthesis of analogous pyrazole compounds,[13] we devised a concise route for key precursor **4** (Scheme 3). Starting from inexpensive 3-chloromandelic acid, protection of the α-hydroxyacid as

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(11) The *Z* isomer was found to be photosensitive. Light exclusion was necessary during the hydrolysis process.
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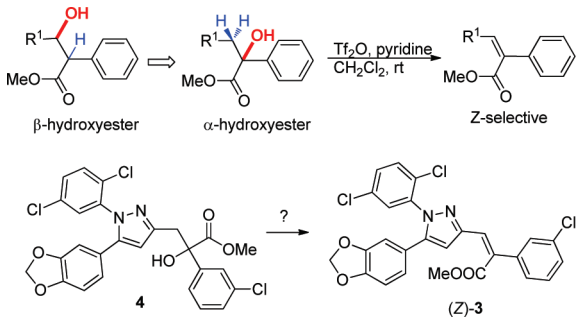
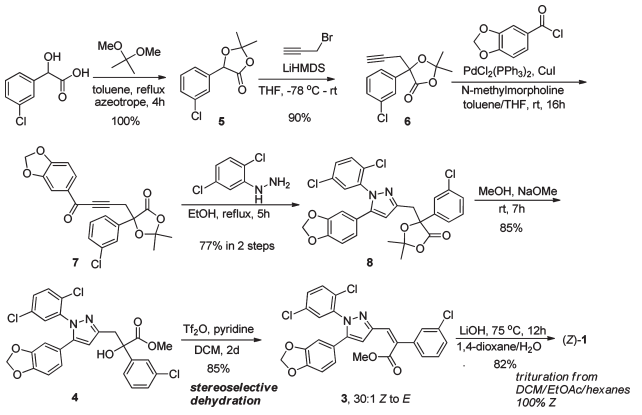


FIGURE 1. The alternative dehydration strategy.

SCHEME 3. Second-Generation Synthesis of Compound (*Z*)-1



a 1,3-dioxolanone followed by a base-mediated alkylation with propargyl bromide afforded **6** in excellent yield. Sonogashira cross-coupling reaction of **6** with 1,3-benzodioxole-5-carbonyl chloride followed by pyrazole formation reaction with 2,5-dichlorohydrazine provided compound **8** in 77% yield over 2 steps. It is worth noting that the pyrazole formation reaction was highly regiospecific with only the desired regioisomer isolated. Deprotection of the 1,3-dioxolanone ring provided the requisite α-hydroxyester precursor **4** in good yield. Gratifyingly, we found that the standard stereoselective dehydration conditions (Tf_2O, pyridine, DCM) developed previously worked well with compound **4** to provide an excellent 30:1 *Z* to *E* selectivity and 85% isolated yield of **3** on multigram scales. At last, the same stereoselective hydrolysis protocol afforded (*Z*)-**1** in excellent yield and selectivity. After trituration from DCM/EtOAc/hexanes, pure compound (*Z*)-**1** was obtained in 7 linear steps and in a 41% overall yield.

In conclusion, two synthetic routes were developed during large-scale synthetic campaigns of compound (*Z*)-**1**, a selective CCK_1 receptor antagonist. The classic Horner−Wadsworth−Emmons reaction and its variants provided modest *Z*−*E* stereoselectivity (3:1) for the construction of the trisubstituted olefin. A stereoselective hydrolysis was then developed for nonchromatographic isolation of the *Z* isomer. The second route capitalized on the novel stereoselective α-hydroxyester dehydration reaction and the regioselective pyrazole synthesis previously developed in this lab to formulate a new synthetic strategy. In the end, compound (*Z*)-**1** was produced from commercially available materials in 7 linear steps with an overall yield of 41%. The whole sequence is high-yielding and amenable for large-scale synthesis.

Experimental Section

HWE Synthesis of Compound 3 (Table 1, 3:1 *Z*:*E* Mixture). In a 250-mL, two-necked, round-bottomed flask, [bis-(2,2,2-trifluoroethoxy)phosphoryl]-(3-chlorophenyl)acetic acid methyl ester (6.5 g, 15.0 mmol, 1.1 equiv) and 18-crown-6 (10.9 g, 41 mmol, 3.0 equiv) were dissolved in anhydrous THF (83 mL). At 0 °C, KOBu^t (1.0 mol/L in THF, 16.5 mL, 1.2 equiv) was added dropwise over 15 min. After the mixture was stirred at 0 °C for 0.5 h, 5-benzo[1,3]dioxol-5-yl-1-(2,5-dichloro-phenyl)-1*H*-pyrazole-3-carbaldehyde **2** (5.0 g, 13.8 mmol, 1.0 equiv) was added portion wise as a solid. Upon completion of the addition, the reaction solution was stirred at room temperature overnight. Saturated NH_4Cl aqueous solution (50 mL) was added to quench the reaction and the resulting suspension was filtered through a pad of Celite and washed with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield **3** as a red-brown oil (7.3 g, 13.8 mmol, 100%) as a mixture of 3:1 *Z*:*E* isomers (the isomeric ratio was determined by the ^{1}H NMR peak integration of the crude product).

Stereoselective Hydrolysis to Remove (*E*)-1 (Scheme 2). In a 250-mL, round-bottomed flask, the 3:1 *Z*:*E* mixture of compound **3** (7.3 g, 13.8 mmol, 1.0 equiv) was dissolved in THF/MeOH (3:1, 120 mL) and the LiOH (0.66 g, 0.027 mol, 2.0 equiv) solution in water (30 mL) was added. After the mixture was stirred at room temperature for 3 h, 1 mol/L of HCl was added to adjust the pH to 4. The organic solvents (MeOH and THF) were removed under vacuum and the remaining aqueous solution was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude oily product was directly loaded onto a short pad of silica gel and washed with 10−20% EtOAc/hexanes to isolate pure ester (*Z*)-**3** (4.9 g, 67% yield) as a pale yellow oil.

Second-Generation Synthesis of Compound (*Z*)-1 (Scheme 3): Compound 8 In a 500-mL, one-necked, round-bottomed flask fitted with a reflux condenser and magnetic stir bar was charged compound **7** (crude, 22.6 g, 56 mmol, 1.0 equiv) prepared in the previous step (see the Supporting Information), then EtOH (300 mL) was added. To this suspension was added 2,5-dichlorophenylhydrazine (10 g, 56.5 mmol, 1.0 equiv) as a solid. The resulting suspension was heated to form a homogeneous solution and stirred at reflux temperature under air for 5 h (end point based on periodic HPLC analysis of the reaction). The solution was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude product was passed through a short pad of silica gel with 10% EtOAc/hexanes as eluents and then recrystallized from hot MeOH to afford pure **8** as a white solid (24.2 g, 42.3 mmol, 77%, for 2 steps). Mp 152−153 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 7.68−7.62 (m, 1 H), 7.38−7.30 (m, 5 H), 6.70 (d, J = 8.2 Hz, 1 H), 6.66−6.60 (m, 2 H), 6.36 (s, 1 H), 5.95 (s, 2 H), 3.44 (d, J = 14.6 Hz, 1 H), 3.26 (d, J = 14.6 Hz, 1 H), 1.42 (s, 6 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.1, 147.9, 147.8, 147.75, 145.7, 141.7, 138.8, 134.5, 133.1, 131.1, 130.4, 130.3, 130.0, 129.8, 128.4, 125.4, 123.5, 123.2, 121.9, 110.9, 108.5, 108.2, 107.0, 101.3, 82.9, 40.7, 27.9, 27.5. HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{28}H_{22}N_2Cl_3O_5$ 571.0589, found 571.0570.

Compound 4. In a 1-L, round-bottomed flask, compound **8** (20.2 g, 0.035 mol, 1.0 equiv) was dissolved in anhydrous methanol (500 mL) and NaOMe (2.10 g, 0.039 mol, 1.1 equiv) was added in one portion. After the mixture was stirred at room temperature overnight, water (500 mL) was added. The reaction mixture was extracted with EtOAc (3 × 200 mL). The organic

layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was passed through a short pad of silica gel with 25% EtOAc in hexanes as the eluents to yield pure **4** as a light yellow oil (16.4 g, 0.030 mol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.59 (dt, J = 6.9, 2.0 Hz, 1H), 7.43−7.27 (m, 5H), 6.75−6.55 (m, 3H), 6.32 (s, 1H), 5.96 (s, 2H), 4.73 (s, 1H), 3.74 (s, 3H), 3.70 (d, J = 14.7 Hz, 1H), 3.26 (d, J = 14.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 149.8, 148.4, 148.2, 145.9, 143.5, 139.1, 134.8, 133.4, 131.6, 131.3, 130.8, 130.3, 130.0, 128.5, 126.5, 124.3, 123.6, 122.5, 108.9, 108.7, 107.4, 101.8, 78.4, 53.7, 39.4. HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{26}H_{19}Cl_3N_2O_5$ 545.0432, found 545.0441.

Compound 3 (30:1 *Z*:*E*). In a 500-mL, round-bottomed flask, compound **4** (16.38 g, 0.030 mol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (160 mL). At 0 °C under N_2, triflic anhydride (16.9 g, 0.060 mol, 2.0 equiv) was added dropwise. After the mixture was stirred for 10 min, anhydrous pyridine (11.8 g, 0.15 mol, 5.0 equiv) was added dropwise. The reaction solution was stirred at 0 °C for 1 h and then warmed to room temperature for another 48 h. Water (250 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (eluting with a gradient of 10−25% EtOAc/hexanes) to yield **3** with 30:1 Z to E selectivity (determined by ^{1}H NMR) as a light orange foam (14.0 g, 88% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50−7.44 (m, 2H), 7.39−7.34 (m, 3H), 7.33−7.28 (m, 2H), 7.05 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.69−6.64 (m, 2H), 6.60 (s, 1H), 5.96 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.0, 148.3, 148.1, 147.8, 146.0, 138.6, 138.2, 134.7, 133.7, 133.1, 131.3, 130.55, 130.46, 130.0, 129.8, 128.4, 126.4, 124.5, 123.6, 123.1, 122.2, 108.5, 108.3, 105.8, 101.4, 52.6. HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{26}H_{18}Cl_3N_2O_4$ 527.0327, found 527.0349.

Compound (*Z*)-1. To a 500-mL, round-bottomed flask were added compound **3** (14.0 g, 0.0265 mol, 1.0 equiv), 1,4-dioxane (140 mL), water (140 mL), and LiOH (3.17 g, 0.132 mol, 5.0 equiv) sequentially. The flask was then submerged into a preheated oil bath at 75−77 °C for 12 h.[14] After the reaction was complete, the reaction solution was cooled to 0 °C and the pH was adjusted to ∼4 with 6 N HCl. The acidified solution was extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with brine, dried over MgSO4, filtered, and concentrated.[15] The crude product was dissolved in CH_2Cl_2 (100 mL) and 10% EtOAc in hexanes (100 mL) was slowly added with stirring. Precipitation began immediately. The stir bar was removed and the flask was left undisturbed at room temperature for several hours. The solids were collected and dried in a vacuum oven at 60 °C to yield the title compound (11.1 g, 82% yield) as an off white crystalline powder. Mp 174−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.47 (m, 1H), 7.46−7.35 (m, 4H), 7.35−7.28 (m, 2H), 7.05 (s, 1H), 6.76−6.71 (m, 1H), 6.70 (s, 1H), 6.69−6.64 (m, 2H), 5.98 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 148.6, 148.0, 147.5, 146.6, 140.9, 137.4, 134.6, 134.1, 133.4, 131.5, 131.2, 130.4, 129.6, 129.4, 128.3, 128.2, 126.7, 126.5, 122.4, 121.9, 108.7, 108.5, 108.3, 101.6. HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{25}H_{16}Cl_3N_2O_4$ 513.0170, found 513.0195.

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Supporting Information Available: General methods, synthetic procedures for the Still-Gennari phosphonate and compounds **5**−**7**, and NMR spectra of compounds **1** and **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Preheating the oil bath is important to avoid significant isomerization. At lower temperatures, the hydrolysis process is very slow so that the isomerization is favored.

(15) A small amount (∼3%) of the undesired E isomer was always observed in the crude final material.