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Synthesis of a new microbial secondary metabolite: anti-*Helicobacter pylori* CJ-13,015☆,☆☆

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Abstract—A six-step, first synthesis of an anti-*Helicobacter pylori* secondary metabolite, CJ-13,015 (**1a**), in 65% overall yield, is described, starting from 5-methylfurfural (**2**), via a Wittig reaction of the ylide generated in situ from (8-hydroxyoctyl)triphenylphosphonium bromide, selective reduction of the newly formed carbon–carbon double bond, conversion of the alcohol to a halide, coupling with the anion of 3,5-dimethoxyphthalide and a chemoselective conversion of the protective furan group to a 1,4-dicarbonyl system as a key reaction.

Gastric and duodenal ulcers affect a significant portion of the human population worldwide. The root cause of gastric and duodenal ulcers is the presence of the microaerophilic Gram-negative bacterium *Helicobacter pylori*, which appear to live beneath the mucus layer of the stomach.[1,2] Current therapy is not entirely successful in achieving long-term eradication of *H. pylori* and relapse is a problem.[1,2] However, long-term treatment with current therapies is not recommended and, accordingly, there is a need for a safe and effective treatment with a compound having an excellent anti-*H. pylori* activity. Recently, in a screening programme designed to discover such compounds, Dekker et al.[3] isolated the new phthalides **1a**–**g** from the basidiomycete *Phanerochaerte velutina* with promising anti-*H. pylori* activity (Table 1). These secondary metabolites **1a**–**g** were isolated in very small amounts and a realistic supply of these natural products for further biological evaluation was required. In continuation of our ongoing studies[4] on the synthesis of recently isolated bioactive natural products, we report herein the first total synthesis of CJ-13,015 (**1a**) (Scheme 1).

The retrosynthetic analysis of the microbial secondary metabolite CJ-13,015 revealed that 5-methylfurfural,[5] 8-bromo-1-octanol[6] and 3,5-dimethoxyphthalide[7] would be suitable building blocks to access **1a**. The Wittig reaction of 5-methylfurfural (**2**) with the ylide generated in situ from the reaction of (8-hydroxyoctyl)triphenylphosphonium bromide and sodium methylsulfinylmethanide in a mixture of DMSO–THF (1:1) furnished the *Z*- and *E*-isomers **3** in an 82% yield. Palladium on charcoal induced selective catalytic hydrogenation of the newly generated carbon–carbon double bond in **3** gave the furan derivative **4** in quantitative yield. The primary alcohol **4** was treated with *p*-toluenesulfonyl chloride to form the corresponding tosylate **5** (96% yield), which, on reaction with lithium bromide, yielded the desired furan-containing alkyl halide **6** in 95% yield. The halide **6** underwent a smooth S_N2 substitution reaction with the anion of 3,5-dimethoxyphthalide in THF at 50 °C to yield the desired coupled product **7** in 90% yield. The furan moiety in compound **7** underwent a clean chemoselective hydrolysis in a refluxing acetic acid–water mixture (1:1) in the presence of a catalytic amount of dilute sulfuric acid to furnish, exclusively, the desired bioactive natural product CJ-13,015 (**1a**), in quantitative yield. Starting from 5-methylfurfural (**2**), 14-(1,3-dihydro-4,6-dimethoxy-3-oxo-1-isobenzofuranyl)-2,5-tetradecanedione (**1a**) was obtained in six steps and in 65% overall yield. The analytical and spectral data obtained

Keywords: Microbial secondary metabolite CJ-13,015; anti-*Helicobacter pylori*; 5-Methylfurfural; Coupling reactions; Furan to 1,4-dicarbonyl system; Total synthesis.
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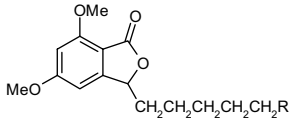
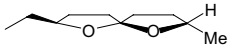
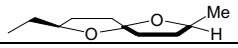
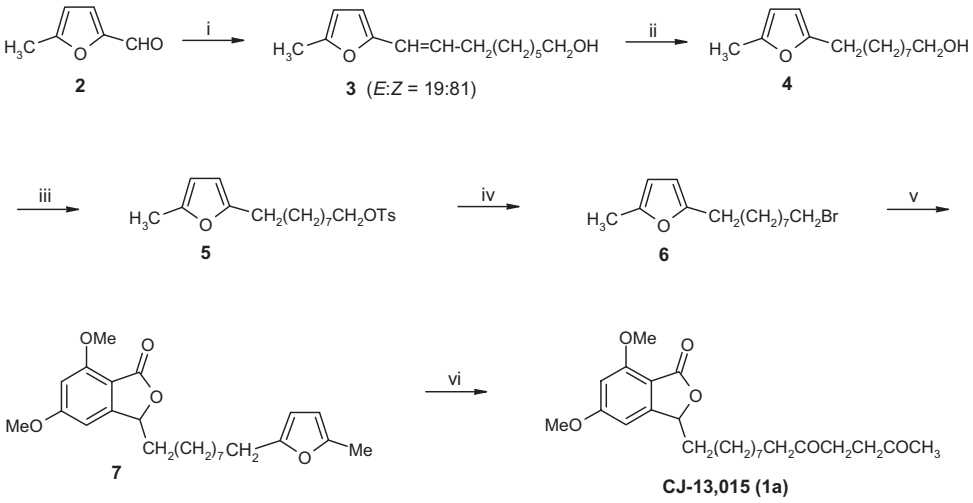
Table 1. New microbial secondary metabolities and their helicobactericidal activities



1a-g

Compound	R	Activity (μg/disk that gives a 15 mm zone)
CJ-13,015 (**1a**)	$-CH_2CH_2CH_2CH_2COCH_2CH_2COCH_3$	2
CJ-13,102 (**1b**)	$-CH_2CH_2CH_2CH_2CH(OAc)CH_2CH_2COCH_3$	0.5
CJ-13,103 (**1c**)	$-CH_2CH_2CH_2CH_2CH_2CH_2COCH_2COCH_3$	50
CJ-13,104 (**1d**)	$-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH(OH)CH_3$	500
CJ-13,108 (**1e**)	$-CH_2CH_2CH_2CH_2CH_2CH_2CH_2COCH_3$	10
CJ-12,954 (**1f**)		0.02
CJ-13,104 (**1g**)		0.02



Scheme 1. Reagents, conditions and yields: (i) $HOCH_2(CH_2)_6CH_2{}^+PPh_3Br^-$ (1.1 equiv), $Na^+CH_2{}^-SOCH_3$ (2.2 equiv), DMSO–THF (1:1), 0 °C, 1 h (82%); (ii) H_2, Pd–C, methanol, rt, 4 h (98%); (iii) *p*-TsCl (1.1 equiv), TEA (2.2 equiv), DMAP, DCM, rt, 6 h (96%); (iv) LiBr (8 equiv), $NaHCO_3$ (10 equiv), acetone, rt, 15 h (95%); (v) (a) 3,5-dimethoxyphthalide (1.5 equiv), LDA (1.5 equiv), THF, 0 °C to rt, 30 min, (b) **6** (1 equiv), 50 °C, 1 h, aq workup, (90%); (vi) H_2O–AcOH (1:1), cat. H^+/H_2SO_4 (dil), reflux, 2 h, (98%).

for CJ-13,015 (**1a**)[8] were in complete agreement with the reported data.[3]

In summary, we have demonstrated a simple and efficient total synthesis of the anti-*H. pylori* microbial secondary metabolite, CJ-13,015 in six steps and in 65% overall yield. In the present synthesis, the use of furan to introduce the 1,4-dicarbonyl system is noteworthy. We feel that the present approach is general and may be employed to design several natural and unnatural analogues of this secondary metabolite. Starting from **3**, our work on the total synthesis of the more active secondary metabolites CJ-12,954 (**1f**) and CJ-13,014 (**1g**) is in progress.

Supplementary material

Analytical and spectral data for compounds **3**–**7** are included.

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8. 14-(1,3-Dihydro-4,6-dimethoxy-3-oxo-1-isobenzofuranyl)-2,5-tetradecanedione (CJ-13,015, **1a**). Mp 104–106 °C (white crystalline solid); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.25 (b s, 8H), 1.25–1.37 (m, 2H), 1.37–1.50 (m, 2H), 1.55 (quintet, $J = 10$ Hz, 2H), 1.63–1.73 (m, 1H), 1.92–2.01 (m, 1H), 2.17 (s, 3H), 2.43 (t, $J = 10$ Hz, 2H), 2.63–2.72 (m, 4H), 3.89 (s, 3H), 3.94 (s, 3H), 5.28 (m, 1H), 6.40 (s, 1H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.79, 24.59, 29.09, 29.24 (four carbons), 29.82, 34.81, 36.03, 36.89, 42.76, 55.86, 55.95, 79.84, 97.53, 98.67, 107.07, 155.19, 159.68, 166.69, 168.30, 207.04, 209.45; IR (Nujol) ν_{max} 1759, 1697, 1614, 1601, 1468, 837 cm^{-1}; Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.92; H, 8.07.