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Chemoselective Coupling Reactions of 5,7-Dimethoxyphthalide with the Remotely Functionalized Alkyl Iodides: Facile Racemic Synthesis of *Helicobacter pylori* Antibiotics

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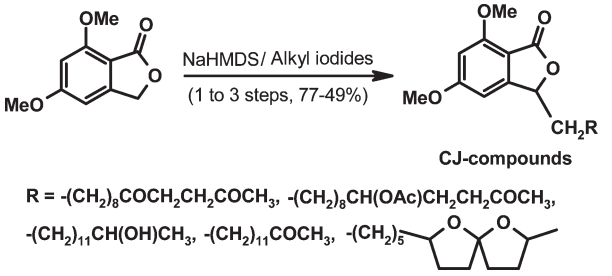
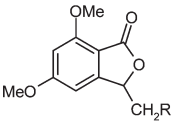


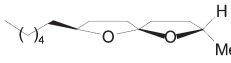
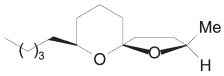
Highly chemoselective coupling reactions of 5,7-dimethoxyphthalide carbanion with the remotely functionalized long chain alkyl iodides have been demonstrated to accomplish the concise and efficient synthesis of *Helicobacter pylori* antibiotics, the CJ-molecules, and sporotricale methyl ether.

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] There is a need for a safe and effective treatment with a compound having an excellent anti-*H. pylori* activity. In a screening program 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). In continuation of our ongoing studies[4] on the synthesis of recently isolated bioactive natural products, we have reported the first total synthesis of CJ-13,015 (**1a**) using furan as the protected source of remotely placed

TABLE 1. New Microbial Secondary Metabolites and Their Helicobactericidal Activities



1a-g

Compound	R	Activity (μg/disk that gives a 15 mm zone)
CJ-13,015 (**1a**)	$-(CH_2)_8COCH_2CH_2COCH_3$	2
CJ-13,102 (**1b**)	$-(CH_2)_8CH(OAc)CH_2CH_2COCH_3$	0.5
CJ-13,103 (**1c**)	$-(CH_2)_{10}COCH_2CH_2COCH_3$	50
CJ-13,104 (**1d**)	$-(CH_2)_{11}CH(OH)CH_3$	500
CJ-13,108 (**1e**)	$-(CH_2)_{11}COCH_3$	10
CJ-12,954 (**1f**)		0.02
CJ-13,014 (**1g**)		0.02
Spirolaxine methyl ether (**1h**)		Not determined

1,4-dicarbonyl system.[5] Recently, Brimble et al. have reported the synthesis of five CJ-compounds **1a**−**e** using an intrinsic flexible approach.[6] Soon after, Dallavalle et al. reported the synthesis of analogues natural product sporotricale methyl ether (**25**).[7] Several elegant syntheses of more challenging target molecules **1f**−**h** with the spiro units have been reported recently.[8] A careful scrutiny of structures of all the CJ-molecules revealed that they are the remotely monofunctionalized, bifunctionalized, and latent trifunctionalized 3-alkyl-substituted 5,7-dimethoxyphthalides. The phthalides substituted at the C-3 position are found in various naturally occurring compounds and they possess interesting biological activities.[9] Synthesis of 3-substiuted phthalides is a challenging task of current interest.[10] Atom economy and the reaction selectivity are the real keys for the synthetic efficiencies.[11] Now, herein we report a concise and efficient approach to the target compounds by taking advantage of highly chemoselective coupling reactions of 5,7-dimethoxyphthalide carbanion with the remotely functionalized tailored long chain alkyl iodides (Schemes 1 and 2).

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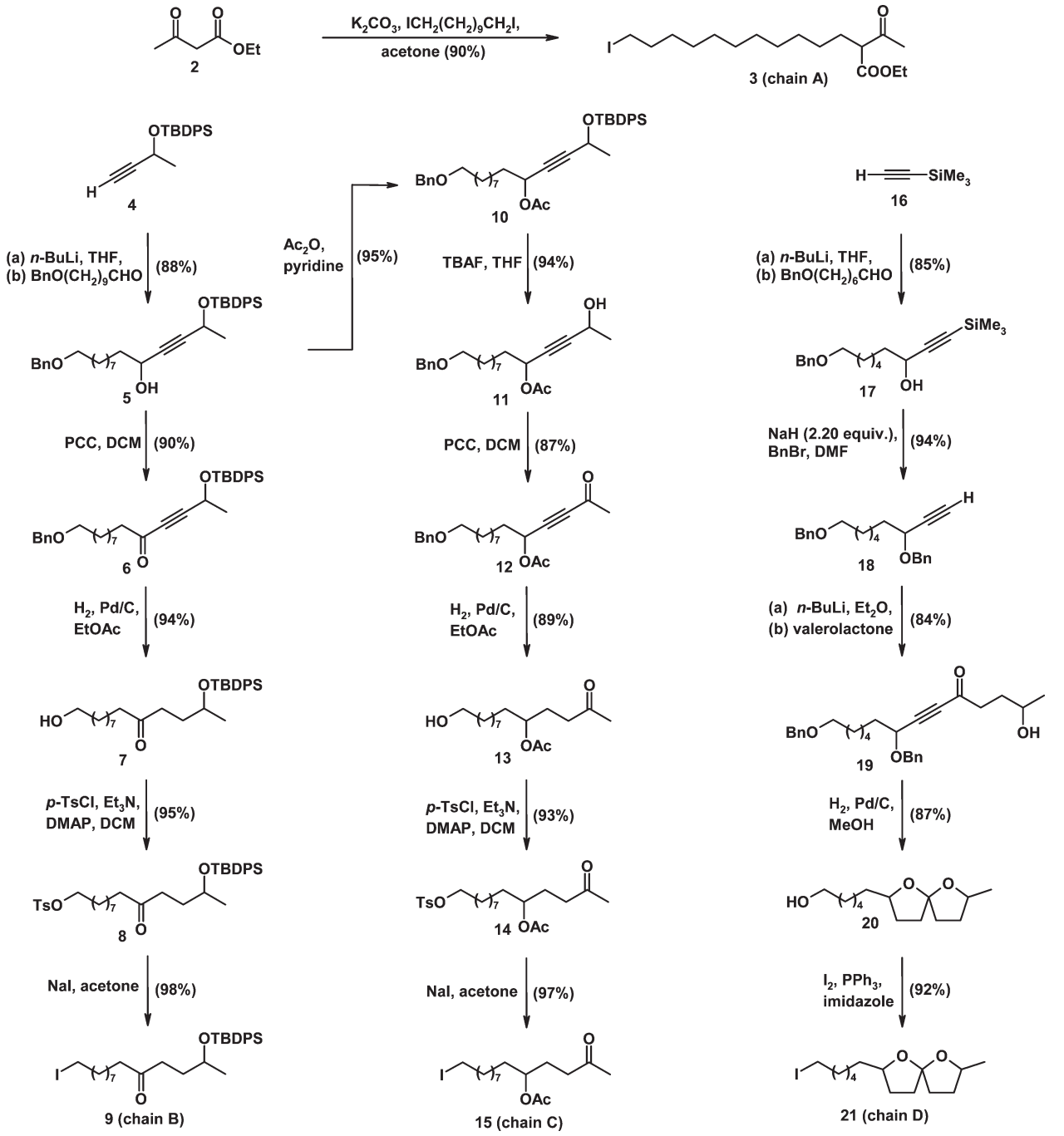
SCHEME 1. Synthesis of Remotely Functionalized Long Chain Alkyl Iodides A−D



We envisaged the stepwise preparation of the desired long chain alkyl iodides (A−D) starting from ethyl acetoacetate (**2**) and two different suitably substituted acetylene derivatives **4**/**16** via the alkylation/condensation with aliphatic aldehydes, followed by the systematic functional group interconversions (Scheme 1). The base-catalyzed selective monocoupling of ethyl acetoacetate with 1,11-diiodoundecane in refluxing acetone furnished the desired chain A in 90% yield. The base-catalyzed coupling of OTBDPS-protected acetylene derivative **4** with the *ω*-*O*-benzyl-protected aliphatic aldehyde followed by the PCC-oxidation of thus formed secondary alcohol furnished the ketone **6**.

(9) (a) Lin, G.; Chan, S. S.-K.; Chung, H.-S.; Li, S.-L. Chemistry and Biological Action of Natural Occurring Phthalides. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, The Netherlands, 2005; Vol. 32, p 611 and references cited therein . (b) Palermo, J. A.; Brasco, M. V. R.; Spagnuolo, C.; Seldes, A. M. *J. Org. Chem.* **2000**, *65*, 4482 and references cited therein. (c) Brady, S. F.; Wagenaar, M. M.; Singh, M. P.; Janso, J. E.; Clardy, J. *Org. Lett.* **2000**, *2*, 4043 and references cited therein. (d) Yoganathan, K.; Rossant, C.; Ng, S.; Huang, Y.; Butler, M. S.; Buss, A. D. *J. Nat. Prod.* **2003**, *66*, 1116 and references cited therein.

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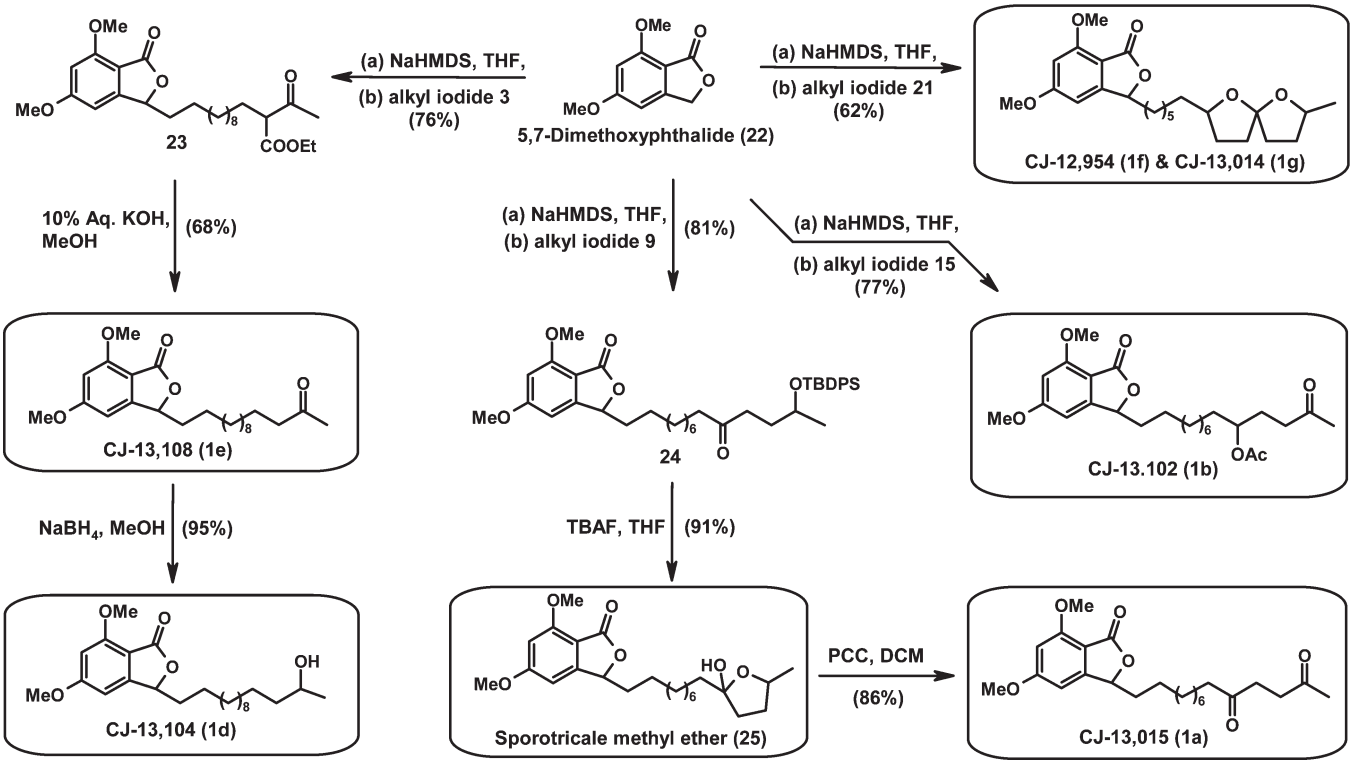
SCHEME 2. Chemoselective Alkylation of 5,7-Dimethoxyphthalide: Synthesis of CJ-Compounds



The ketone **6** on catalytic hydrogenation underwent both the debenzylation and reduction of carbon−carbon triple bond in one pot to provide the reduced desired product **7**. The silyl-protected keto-alcohol **7** on tosylation followed by treatment with sodium iodide gave the desired chain B with 69% overall yield in five steps. The common intermediate **5** on acylation followed by desilylation gave the secondary alcohol **11**, which on PCC-oxidation gave the ketone **12**. The ketone **12** on catalytic hydrogenation gave the expected debenzylated reduced product **13**, which on tosylation followed by treatment with sodium iodide gave the desired chain C with 51% overall yield in seven steps. Trimethylsilylacetylene (**16**) on reaction with the *O*-benzyl-protected requisite aliphatic aldehyde followed by benzyl protection of the formed secondary alcohol directly furnished an in situ desilylated acetylene derivative **18**. Compound **18** on base-catalyzed condensation with the γ-valerolactone provided the keto-alcohol **19**. The product **19** on catalytic hydrogenation formed the double debenzylated saturated ketone as an unstable intermediate, which on rapid intramolecular dehydrative double cyclization provided the spiro-alcohol **20**. The alcohol **20** on treatment with iodine and triphenylphosphine gave the desired chain D with 54% overall yield in five steps. Thus we accomplished the smooth preparation of the desired remotely functionalized alkyl iodide long chains A−D in a concise and efficient fashion via the appropriate functional group interconversion pathways.

The phthalides are widely used building blocks in organic synthesis and the generated benzylic carbanions on them are known to react with acid chlorides, imines, alkyl halides, aldehydes, and esters.[5,12] The preferred reactivity of phthalide carbanions toward S_N2-displacements of halides versus addition to the carbonyl groups has not been studied previously. The alkyl iodide chains A−D contain remotely placed ketone/ester, silyloxyketone, acetoxyketone, and spiroketal units, respectively. We developed a systematic plan to generate a 5,7-dimethoxyphthalide carbanion and study its chemoselective coupling reactions with the primary alkyl iodide chains A−D, with the expectation that the stabilized benzylic carbanion will be competing for an S_N2 substitution reaction over the 1,2-addition reactions (Scheme 2). We screened bases such as triethylamine, DBU, NaH, *n*-BuLi, *s*-BuLi, LDA, and NaHMDS for the generation of the necessary benzylic carbanion on phthalide **22** and studied the chemoselective coupling reactions with the primary alkyl iodide chain A under a similar set of reaction conditions. In our hands, the bases triethylamine, DBU, NaH, and *n*-BuLi were ineffective in inducing the coupling of phthalide **22** with the alkyl iodide chain A (**3**). The use of *s*-BuLi as the base for the coupling of **22** with iodide **3** formed the desired product **23**, but only in 5% to 6% yield. The use of LDA also gave the desired product with 41% yield along with the formation of some side products. The best results were obtained with the bulky NaHMDS as the base. The chemoselective reaction of benzylic carbanion from 5,7-dimethoxyphthalide (1.00 equiv), generated by using NaHMDS (1.10 equiv) as the base, with alkyl iodide chain A (1.00 equiv) exclusively furnished the expected

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coupled product **23** in 76% yield via the S_N2-displacement pathway. On the basis of formation of product **23**, we feel that the S_N2-displacement of primary alkyl iodide in chain A with the benzylic carbanion of phthalide **22** is faster than the deprotonation of the acidic methine proton in chain A by the phthalide carbanion. The base-catalyzed hydrolysis of ester moiety in compound **23** followed an in situ decarboxylation of the intermediate β-keto acid furnished the desired bioactive natural product CJ-13,108 (**1e**) in 68% yield. Chemoselective $NaBH_4$-reduction of the ketone moiety in **1e** furnished the desired bioactive natural product in the series, the CJ-13,104 (**1d**), in 95% yield. Similarly, the chemoselective reaction of benzylic carbanion from 5,7-dimethoxyphthalide with chain B furnished the product **24**, which on desilylation gave the natural product sporotricale methyl ether (**25**). In solution the compound **25** displays a ring−chain tautomerism, chloroform (hemiketal)/acetone (hydroxyketone).[7] Compound **25** on PCC-oxidation provided the CJ-13,015 (**1a**) in very good yield. Finally, the chemoselective couplings of the phthalide carbanion with chain C and chain D respectively furnished the desired products CJ-13,102 (**1b**) and a diastereomeric mixture of CJ-12,954/CJ-13,014 (**1f**)/(**1g**). The analytical and spectral data obtained for CJ-13,015 (**1a**), CJ-13,102 (**1b**), CJ-13,104 (**1d**), CJ-13,108 (**1e**), CJ-12,954/CJ-13,014 (**1f**)/(**1g**), and sporotricle methyl ether (**25**) were in complete agreement with the reported data[3,6] and were obtained in one to three steps with very good overall yields. These results clearly demonstrate the preferential S_N2 displacement ability of the NaHMDS-generated phthalide carbanion over the 1,2-addition to carbonyl groups.

In summary, we have reported a practical synthesis of remotely functionalized important natural products, the CJ-molecules, by taking advantage of highly chemoselective carbon−carbon bond forming reactions of phthalide with the functionalized alkyl iodides. We feel that in the present approach, the remarkably chemoselective displacements of primary iodides by the 5,7-dimethoxyphthalide carbanion, specifically in the presence of a free ketone, and ester moieties are noteworthy. Our approach is general in nature and will be useful in designing a focused minilibrary of analogous and congeners of CJ-molecules for SAR studies.

Experimental Section

Ethyl 2-Acetyl-13-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)tridecanoate (23). To a stirred solution of 5,7-dimethoxyphthalide (**22**, 500 mg, 2.57 mmol) in THF (25 mL) at −20 °C was added NaHMDS (1 M in THF, 2.83 mL, 2.83 mmol) and the reaction mixture was stirred at −20 °C for 45 min, which was followed by the dropwise addition of alkyl iodide **3** (chain A, 1.05 g, 2.57 mmol) in THF (8 mL) at −20 °C. The reaction mixture was allowed to attain room temperature. Saturated NH_4Cl solution (5 mL) was added to the reaction mixture and THF was removed in vacuo. To the reaction mixture was added ethyl acetate (20 mL) and the separated organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue with 35% ethyl acetate/petroleum ether as an eluent afforded pure product **23** (932 mg, 76%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (br s, 14H), 1.28 (t, J = 8 Hz, 3H), 1.26−1.38 (m, 2H), 1.38−1.52 (m, 2H), 1.62−1.74 (m, 1H), 1.77−1.91 (m, 2H), 1.93−2.05 (m, 1H), 2.23 (s, 3H), 3.40 (t, J = 8 Hz, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 4.20 (q, J = 8 Hz, 2H), 5.30 (dd, J = 8 and 2 Hz, 1H), 6.42 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 24.5, 27.3, 28.1, 28.7, 29.2, 29.3, 29.36, 29.42, 34.7, 55.8, 55.9, 59.8, 61.1, 79.9, 97.3, 98.5, 106.7, 155.1, 159.4, 166.6, 168.5, 169.8, 203.4; IR ($CHCl_3$) ν_{max} 1746, 1721, 1712, 1605 cm^{-1}. Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.71; H, 8.60.

Similarly, the reactions of phthalide **22** with alkyl halide chains B−D respectively furnished the corresponding products **24**, **1b**, and **1f**/**g** (see the Supporting Information).

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Supporting Information Available: Experimental procedures and the tabulated analytical and spectral data for the compounds **1a**, **1b**, **1d**, **1e**, **1f**/**g**, **3**, **5**−**15**, **17**−**21**, and **23**−**25** and ^1H NMR, ^{13}C NMR, and DEPT spectra of compounds **1a**, **1b**, **1d**, **1e**, **1f**/**g**, **3**, **5**−**15**, **17**−**21**, and **23**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.