Synthesis of Benzotriazole Analogues of the Helicobactericidal Agents CJ-13,015, CJ-13,102, CJ-13,108, and CJ-13,104 Using a Regioselective 1,3-Dipolar Cycloaddition

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Received 19 October 2010

Abstract: A regioselective 1,3-dipolar cycloaddition of a disubstituted aryne and various alkyl azides facilitates access to benzotriazole analogues of several anti-*Helicobacter pylori* antibiotics.

Key words: benzotriazole, helicobacter pylori, benzyne, dipolar cycloaddition

Helicobacter pylori has been shown by epidemiological studies to have an etiological role in several diseases, including gastric and duodenal ulcers, distal gastric cancer, mucosal-associated lymphoid tissue (MALT) lymphoma (cancer of the B cell lymphocytes), and was implicated in the cause of 5.6% of all cancers worldwide in 2002.[1] This microaerophilic, Gram-negative bacterium[2] has been estimated to infect the stomach of over half of the world's population making it the planet's most widespread infection.[3] In the majority of cases, infection will persist for the lifetime of an individual in the absence of medical intervention.[4]

Current treatments for *H. pyroli* infections are complex and rely on broad range antibiotics in combination with proton-pump inhibitors and bismuth salts.[5] The first line of treatment cures less than 20% of patients due to unpleasant side effects which often leads to noncompliance.[5] *H. pyroli* also quickly develops resistance to the currently used antibiotics clarithromycin and metronidazole.[5] The complex nature of current treatments combined with their often poor success rates and side effects dictates an obvious need for new helicobactericidal treatments.[5,6]

In a screening program to isolate such compounds, Dekker and co-workers isolated several new phthalide antibiotics **1**–**6** (Figure 1) with specific anti-*H. pylori* activity from the basidiomycete *Phanerochaete velutina* CL6387.[7] Two structurally related compounds, spirolaxine **7**[8a] and its methyl ether **8**[8b] have been isolated from the cultures of *Phanerochaete chrysosporium* and they have also been shown to be good inhibitors of the *H. pylori* bacterium.[7,12]

The ongoing studies in our laboratory regarding the synthesis of potential anti-*H. pylori* compounds has witnessed the racemic syntheses of CJ-13,015, CJ-13,102, CJ-13,108, CJ-13,104 (**1**–**4**)[9] together with the total synthesis and stereochemical assignment of the complex spiroacetal-containing phthalides CJ-12,954 (**5**), CJ-13,014 (**6**)[10] and spirolaxine methyl ether (**8**).[11] We have also synthesized several indole analogues of the CJ antibiotics (**1**–**4**)[12] that subsequently displayed inhibitory activity against *H. pylori*.[13]

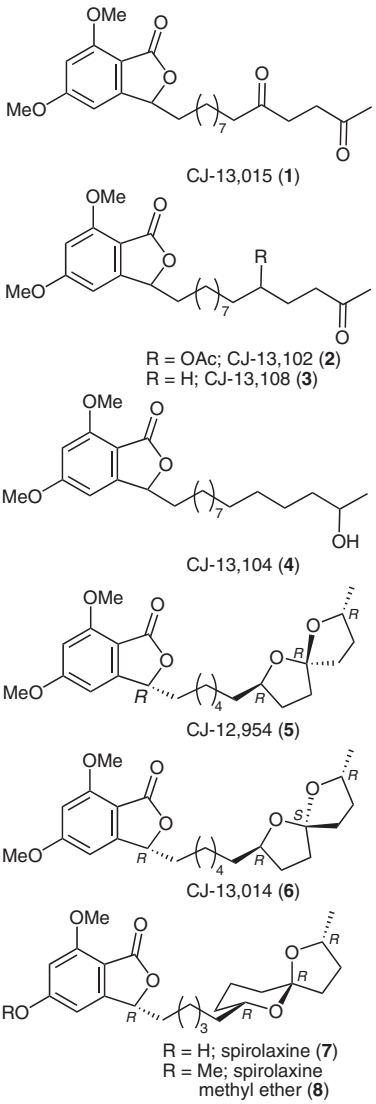
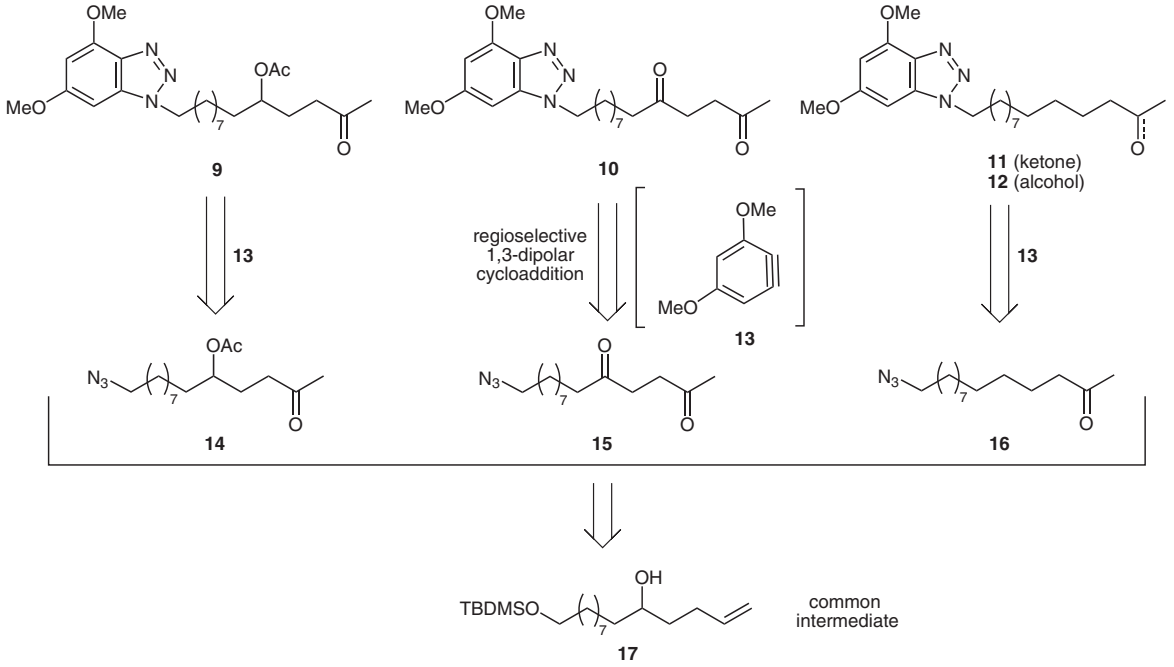


Figure 1 Phthalide containing antibiotics with anti-*H. pylori* activity

SYNLETT 2011, No. 1, pp 0099–0103
Advanced online publication: 07.12.2010
DOI: 10.1055/s-0030-1259081; Art ID: D27810ST



Scheme 1 Proposed synthesis of benzotriazole analogues of selected helicobactericidal compounds

Prompted by our recent observation that indole analogues of **1**–**4** exhibit activity against *H. pylori*,[13] combined with our ongoing interest in the synthesis of triazole analogues of biologically active natural products[14] and natural product-like scaffolds,[15] we decided to undertake the synthesis of benzotriazole analogues of the aforementioned CJ antibiotics **1**–**4** with the idea of improving their bioactivity. We herein describe the convergent synthesis of several benzotriazole analogues of the CJ antibiotics **1**–**4** using a highly regioselective 1,3-dipolar cycloaddition of a dioxygenated benzyne and a range of alkyl azides.

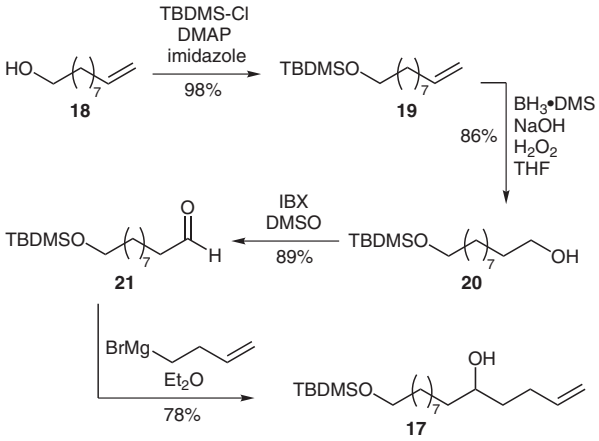
The planned retrosynthesis of the benzotriazole analogues **9**–**12** of the CJ antibiotics **1**–**4** is shown in Scheme 1. It was envisaged that disubstituted benzyne **13** would undergo a regioselective 1,3-dipolar cycloaddition with a series of azides **14**–**16** which in turn would all be available from the same common intermediate **17**. The convergent nature of this proposed route makes it well suited for analogue design (Scheme 1).

The synthesis of the common intermediate **17** is outlined in Scheme 2. Dec-9-en-1-ol (**18**) underwent smooth silylation affording silyl ether **19** which was subjected to standard hydroboration conditions giving alcohol **20**. IBX-mediated oxidation followed by Grignard extension of the resulting aldehyde **21** completed a multigram synthesis of the key intermediate **17** in excellent overall yield (Scheme 2).

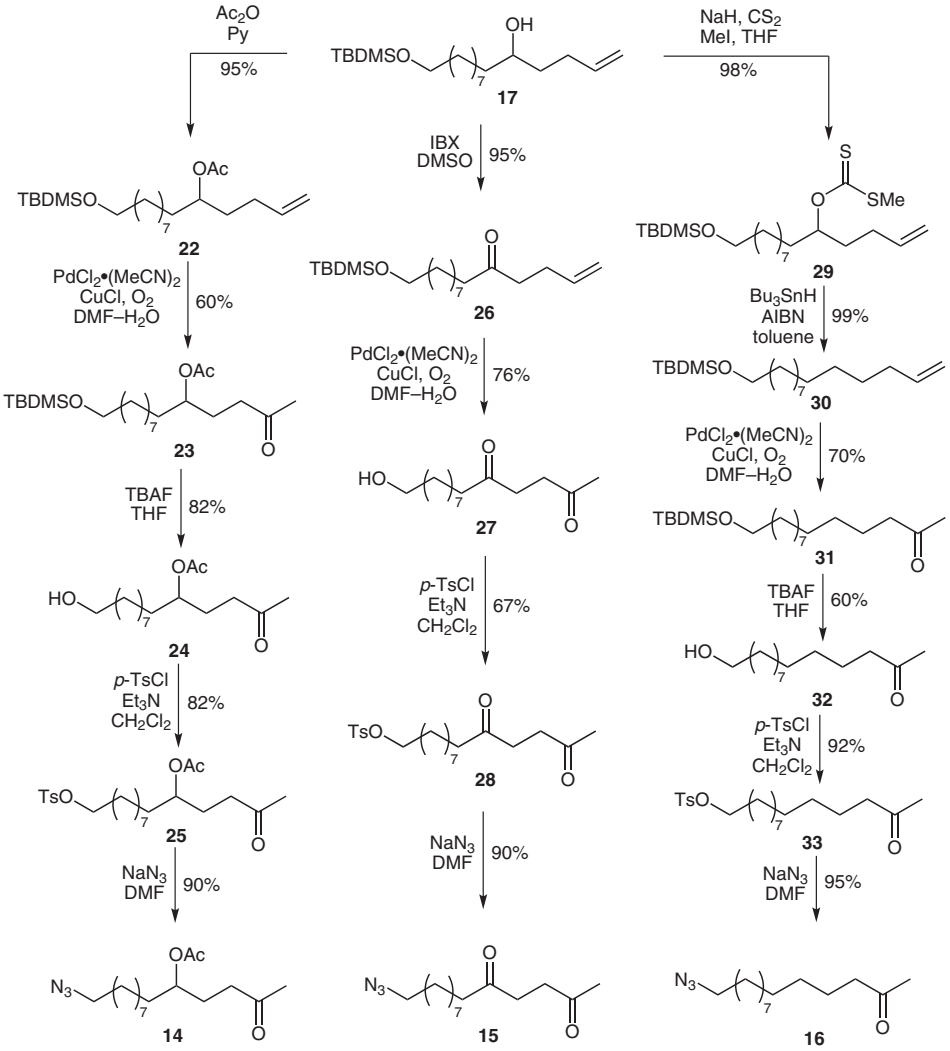
Next, the synthesis of the azides **14**–**16** necessary to complete the synthesis of the CJ antibiotic analogues was undertaken (Scheme 3). Common intermediate **17** was first acetylated to give **22** then subjected to Wacker oxidation conditions affording **23**. Desilylation gave alcohol **24** which was converted into tosylate **25** and subsequently the first azide coupling partner **14**. The alcohol intermediate **17** was oxidized with IBX and the resulting ketone **26** subjected to Wacker oxidation delivering 1,4-diketone **27** that underwent concomitant desilylation. Facile tosylation to **28** and subsequent azide displacement delivered the second azide coupling partner **15**. Finally, the third azide coupling partner **16** was constructed.

Alcohol intermediate **17** was converted into xanthate **29** which underwent Barton–McCombie deoxygenation delivering **30**. Wacker oxidation gave ketone **31** which underwent smooth desilylation to alcohol **32** and azide displacement of the tosylate **33** delivering the final coupling partner **16** (Scheme 3).

Next, attention turned to the key benzyne–azide cycloaddition step. Initial attention focused on the synthesis of model deoxy analogues of the CJ antibiotics **1**–**4** in order to first assess the viability of the proposed cycloaddition



Scheme 2 Synthesis of common intermediate **17**



Scheme 3 Synthesis of azide coupling partners **14**, **15**, and **16**

approach. Accordingly, benzyne precursor **34** ($R^1 = R^2 = H$) was accessed in multigram quantities using a recent literature procedure.[16] Gratifyingly, upon subjecting azide **14** and benzyne precursor **34** to the previously reported 'click' cycloaddition conditions[17] the benzotriazole analogue **35** of CJ-13,102 was obtained in moderate yield (Table 1, entry 1). Azide **15** was also a willing participant in the cycloaddition, delivering benzotriazole analogue **36** of CJ-13,015 in good yield (entry 2). Likewise, azide **16** underwent cycloaddition with benzyne precursor **34** delivering **37** (entry 3), which could be converted into a further analogue **38** (entry 4) by straightforward reduction of **37** with sodium borohydride.

Thus, with the foundations of the cycloaddition concept clearly established by the successful synthesis of four deoxy analogues of the CJ compounds (entries 1–4) our attention turned to the use of a benzyne precursor **39** possessing the requisite 4,6-dimethoxy substitution pattern necessary for the synthesis of the fully substituted analogues **9**–**12**. This would of course investigate the obvious regioselectivity issues arising from the use of unsymmetrical arynes in the key cycloaddition step.[18]

Treatment of the benzyne precursor **39**[18c] with azide **14** under the standard conditions described previously led to a single product in excellent yield. ^{1}H NMR and ^{13}C NMR analysis indicated that only one regioisomer was present in the reaction mixture and a strong NOE correlation between 7-H and 14-CH_2 gratifyingly confirmed the product was the desired regioisomer **9** (Table 1, entry 5, Figure 2). Azide **15** also participated in the benzyne cycloaddition with **39** producing a single regiosiomer, confirmed as **10** by NOE studies (entry 6). Likewise, azide **16** underwent regioselective cycloaddition with benzyne precursor **39** delivering **11** (entry 7), which could be readily converted

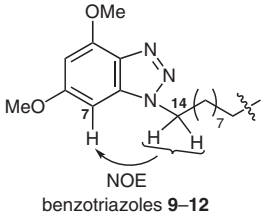
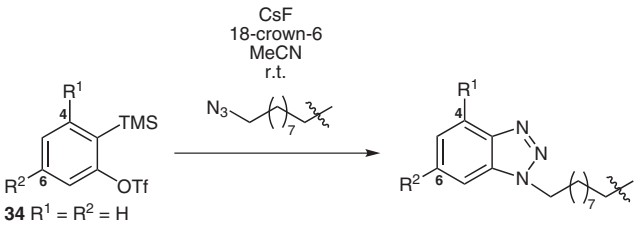
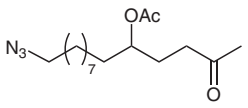
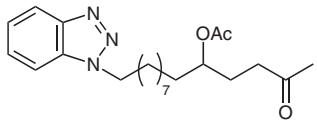
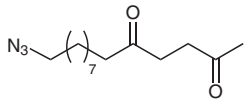
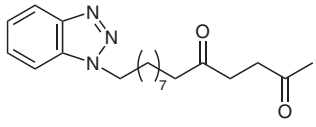
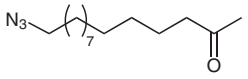
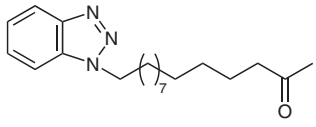
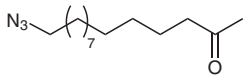
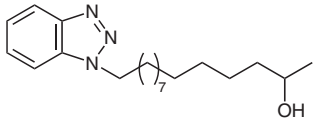
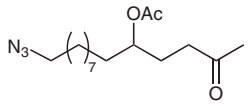
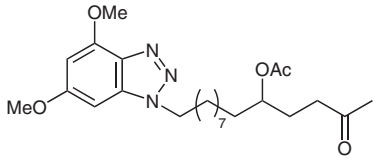
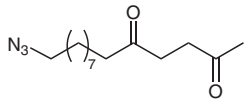
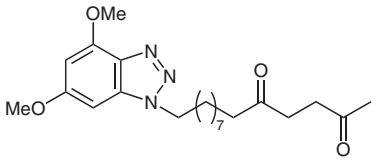
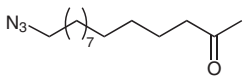
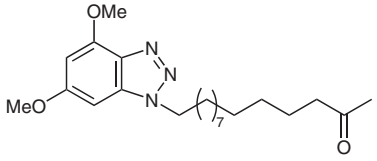
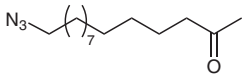
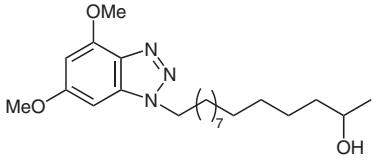


Figure 2 Observed NOE correlation in benzotriazoles **9**, **10**, **11**, and **12**

Table 1 Synthesis of Benzotriazole Analogues of the CJ Antibiotics[19]



34 $R^1 = R^2 = H$
39 $R^1 = R^2 = OMe$

Entry	Benzyne precursor (equiv)	Azide	Time (h)	Product	Yield (%)
1	**34** (3)	 **14**	3	 **35**	54
2	**34** (3)	 **15**	2.5	 **36**	64
3	**34** (3)	 **16**	5	 **37**	26
4	**34** (3)	 **16** then $NaBH_4$, MeOH	5	 **38**	18 (2 steps 26 + 68)
5	**39** (2)	 **14**	2	 **9**	85
6	**39** (2)	 **15**	1.5	 **10**	77
7	**39** (2)	 **16**	4.5	 **11**	72
8	**39** (2)	 **16** then $NaBH_4$, MeOH-THF	4.5	 **12**	67 (2 steps 72 + 93)

into a further analogue **12** (entry 8) by treatment of **11** with sodium borohydride.

In conclusion, we have prepared eight benzotriazole analogues of several CJ antibiotics, four of which were obtained using an entirely regioselective 1,3-dipolar cycloaddition between a disubstituted aryne and the appropriate azide.[19] Biological evaluation of these compounds is in progress and will be reported in due course.

Acknowledgment

We thank the University of Auckland and the Maurice Wilkins Centre for Molecular Biodiscovery for financial support of this work.

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(19) **General Procedure for the Synthesis of Benzotriazole Analogues of the CJ Compounds**
To a stirred solution of azide (0.3 mmol) in MeCN (6 mL) was added CsF (0.6 mmol, 2 equiv) and 18-crown-6 (0.6 mmol, 2 equiv), and the reaction mixture was stirred at r.t. for 15 min. A solution of benzyne precursor **39** (0.6 mmol, 2 equiv) in MeCN (2 mL) was added dropwise, and the reaction mixture was stirred until completion (1.5–5 h). Aqueous $NaHCO_3$ (10 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The resulting residue was purified by flash chromatography using hexanes–EtOAc as eluent to afford the desired benzotriazole (Table 1).