

Synthesis of the spiroacetal-containing anti-*Helicobacter pylori* agents CJ-12,954 and CJ-13,014†

Margaret A. Brimble* and Christina J. Bryant

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The first synthesis of the spiroacetal-containing anti-*Helicobacter pylori* agents *ent*-CJ-12,954 and *ent*-CJ-13,014 is reported based on the union of a heterocycle-activated spiroacetal-containing sulfone fragment with a phthalide-containing aldehyde fragment; comparison of the ¹H and ¹³C NMR data, optical rotations and HPLC retention times of the synthetic compounds (3*S*,2'*S*,5''*S*,7''*S*)-(1a) and (3*S*,2'*S*,5''*R*,7''*S*)-(2a) and the (3*R*)-diastereomers (3*R*,2'*S*,5''*S*,7''*S*)-(1b) and (3*R*,2'*S*,5''*R*,7''*S*)-(2b) with the naturally occurring compounds established that the synthetic isomers (1a) and (2a) were in fact enantiomeric to the natural products CJ-12,954 and CJ-13,014.

Helicobacter pylori is a Gram-negative micro-aerophilic spiral bacterium that resides in the mucus layer above the gastric epithelium¹ and can cause peptic ulcer disease and gastric cancer in humans.² The International Agency for Research on Cancer classified *H. pylori* as a class I carcinogen in 1994.³ A variety of effective drugs for the treatment and eradication of *H. pylori* infection are clinically useful, including antibiotics (β-lactams, macrolides and quinolones), bactericidal agents (bismuth salts), and antiprotozoal agents (metronidazole); however, drug resistance, side effects and non-compliance⁴ prompt development of more effective and selective anti-*H. pylori* agents.

Dekker *et al.*⁵ isolated seven new 5,7-dimethoxyphthalide antibiotics with specific anti-*H. pylori* activity from the basidiomycete *Phanerochaete velutina* CL6387. The two most potent compounds, CJ-12,954 **1** and its C-5'' epimer CJ-13,014 **2**, contained a 5,5-spiroacetal ring joined through a polymethylene chain to the phthalide unit (Fig. 1). While changes in the stereochemistry associated with the spiroacetal have little effect on antibacterial activity, the diketone formed by ring opening exhibits a decreased potency of approximately 100-fold. Two structurally related helicobactericidal compounds, spiroloxine **3** and its methyl ether **4**, contain a 6,5-spiroacetal ring joined through a polymethylene chain to a phthalide unit.⁶ Thus, phthalide-containing spiroacetal compounds provide promising new leads for the treatment of *H. pylori*-related diseases.

Whilst Dekker *et al.*⁵ were unable to assign the stereochemistry of the stereogenic centre at C-3 on the phthalide unit in CJ-12,954 **1** and CJ-13,014 **2**, they were able to assign the relative

stereochemistry of the three stereogenic centres on the spiroacetal ring. CJ-12,954 **1** was assigned with 1,3-*syn* stereochemistry between the C2''-Me group and the C5''-O6'' bond with the 6'-CH₂ group 1,3-*syn* to C5''-O1''. In the case of CJ-13,014 **2** the C2''-Me group was assigned as 1,3-*anti* to the C5''-O6'' bond with the 6'-CH₂ group 1,3-*anti* to the C5''-O1'' bond. The structures of CJ-12,954 **1** and CJ-13,014 **2** were initially arbitrarily depicted with the (*S*)-configuration at both C2'' and C7''; however, the assignment of absolute stereochemistry to these stereogenic centres and C-3 on the phthalide unit requires the synthesis of these natural products which has not been reported to date although several simpler non spiroacetal-containing phthalides have been prepared with lack of stereocontrol of the phthalide unit.⁷⁻⁹

We have reported¹⁰ the synthesis of (+)-spiroloxine methyl ether by coupling a 6,5-spiroacetal moiety of defined stereochemistry with a stereochemically-defined phthalide moiety, thus establishing the absolute stereochemistry of the natural product to be (3*R*,2'*R*,5''*R*,7''*R*). An alternative synthesis in which the stereochemistry at C-3 in the phthalide unit was not controlled necessitated separation of (+)-spiroloxine methyl ether from its C-3 diastereomer by HPLC in the final step.¹¹

We herein report a flexible convergent synthesis of CJ-12,954 and CJ-13,014 initially focusing on the synthesis of (3*S*,2'*S*,5''*S*,7''*S*)-(1a) and (3*S*,2'*S*,5''*R*,7''*S*)-(2a) arbitrarily chosen with the (*S*)-configuration at C-3 on the phthalide unit and at C-2'' and C-7'' in the spiroacetal. The key step involves modified Julia olefination of phthalide-aldehyde **5a** (Scheme 1) with heterocycle-activated sulfones **6** and **7** (Scheme 2).

The (*S*)-stereochemistry at C-3 in phthalide-aldehyde **5a** (Scheme 1) was established by asymmetric reduction of ketone **8**¹² using (*R*)-2-Me-CBS-oxazaborolidine¹³ and borane-dimethyl sulfide affording homoallylic alcohol **9** in 92% yield and 94% e.e.¹⁴

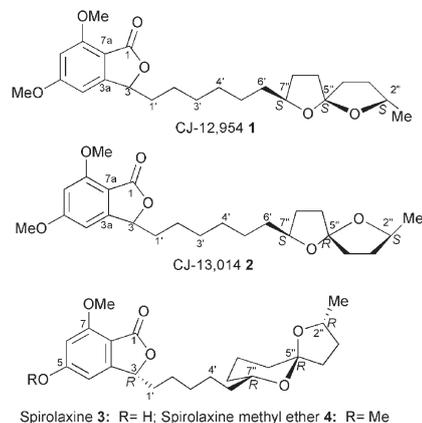
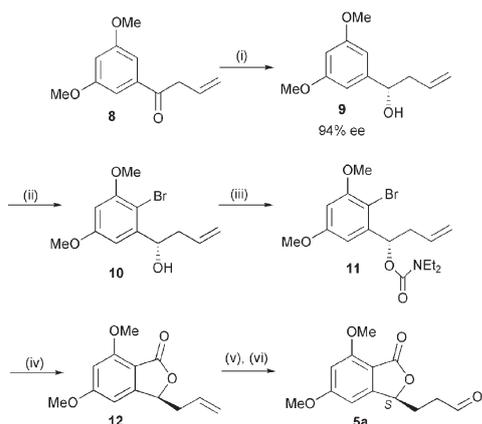


Fig. 1

Department of Chemistry, The University of Auckland, 23 Symonds St., Auckland, New Zealand. E-mail: m.brimble@auckland.ac.nz; Fax: +64 9 3737599; Tel: +64 9 3737599 ext. 88259

† Electronic supplementary information (ESI) available: Experimental section and Fig. S2 depicting key NMR data for **1a/2a** and **1b/2b**. See DOI: 10.1039/b612757f



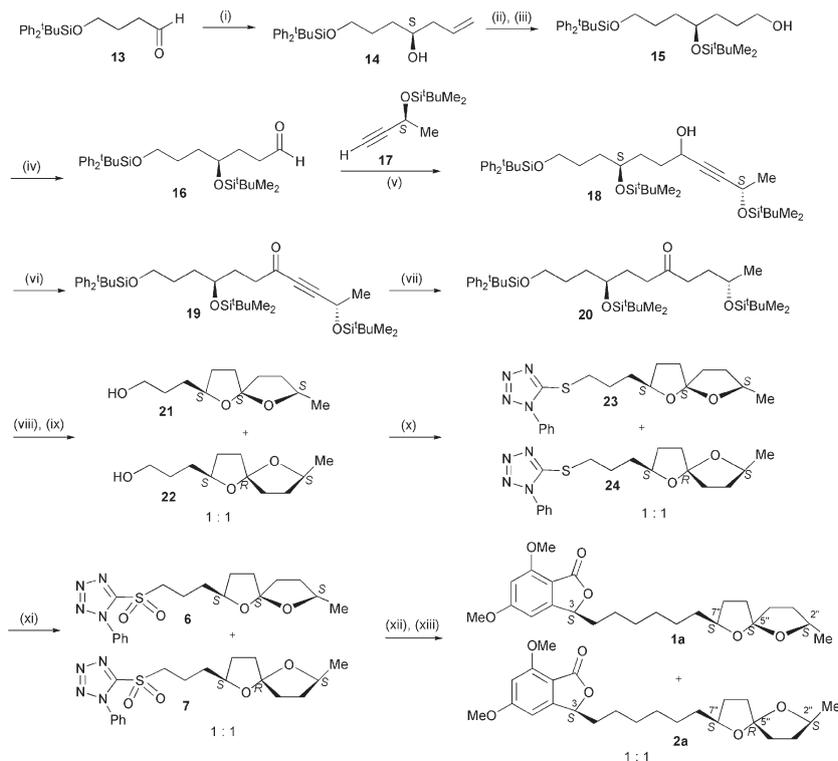
Scheme 1 Reagents and conditions: (i) (*R*)-MeCBS, $\text{BH}_3\text{-SMe}_2$, 15 min, then THF, **8**, 2 h, 92%, 94% ee; (ii) NBS, NH_4OAc , Et_2O , 24 h, 90%; (iii) NaH, THF, 0 °C then *N,N*-diethylcarbamoyl chloride, 90%; (iv) *t*-BuLi, THF, -78 °C, 2 h then camphorsulfonic acid, 20 °C, 12 h, 70%; (v) 2-methyl-2-butene, $\text{BH}_3\text{-SMe}_2$, THF, 0 °C then MeOH, NaOH, 30% H_2O_2 , 71%; (vi) TPAP, NMO, CH_2Cl_2 , 4 Å mol. sieves, 6 h, 20 °C, 72%

Regioselective bromination of the aromatic ring afforded bromide **10** and subsequent conversion to diethyl carbamate **11** facilitated subsequent lithium-halogen exchange and intramolecular acylation to phthalide **12**. Hydroboration of the allyl group followed by oxidation then provided the desired phthalide-aldehyde **5a** in higher optical purity than its antipode which was prepared *via* an asymmetric allylation strategy.¹⁰

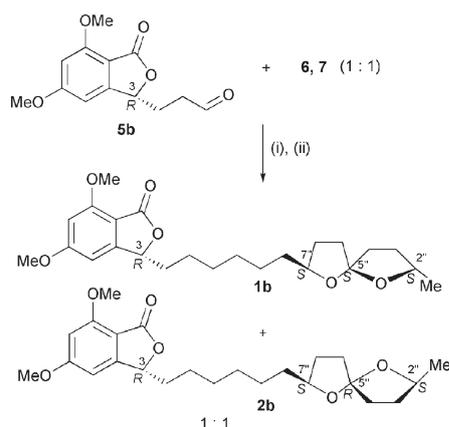
Attention next focused on the synthesis of sulfones **6** and **7** which are epimeric at the spirocentre (Scheme 2). 1-Phenyl-1*H*-tetrazol-5-yl sulfones **6** and **7** were chosen in preference to the use of benzothiazol-2-yl sulfones due to their increased stability in heterocycle-modified Julia olefinations.^{15,16} Lithium (*S*)-acetylide **17**¹⁷ provides access to the 5,5-spiroacetal ring system with (*S*)-stereochemistry at C-2'' and the (7''*S*)-stereochemistry is derived from homoallylic alcohol **14**, available *via* asymmetric allylation of aldehyde **13**.¹⁸

Addition of allylmagnesium bromide to (+)- β -diisopinocampheylmethoxyborane followed by addition of aldehyde **13**¹⁸ afforded (*S*)-alcohol **14**¹⁹ in 82% yield and 94% ee (determined by chiral HPLC†). Silyl ether formation followed by hydroboration and oxidation of the resultant primary alcohol **15** afforded aldehyde **16**. Addition of aldehyde **16** to lithium acetylide **17** at -78 °C in the presence of lithium bromide²⁰ provided alcohol **18** as a mixture of diastereomers that was oxidized to ketone **19** using TPAP and NMO. Reduction of the acetylene over PtO_2 followed by spirocyclisation using camphorsulfonic acid in dichloromethane afforded an inseparable 1 : 1 mixture of spiroacetals **21** and **22** after cleavage of the *tert*-butyldiphenylsilyl ether. Lack of stereocontrol from the anomeric effect²¹ contributed to the observed formation of equal quantities of 5,5-spiroacetals **21** and **22**.

Mitsunobu displacement of hydroxyspiroacetals **21** and **22** with 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3 and DEAD afforded sulfides **23** and **24** that underwent oxidation to an inseparable mixture of sulfones **6** and **7**. Finally the key heterocycle-activated¹⁵ modified



Scheme 2 Reagents and conditions: (i) allyl bromide, Mg, (+)- β -diisopinocampheylmethoxyborane, Et_2O , -78 °C to 20 °C, 82%, 94% ee; (ii) *t*-BuMe₂SiCl, imidazole, DMAP, CH_2Cl_2 , 20 °C, 12 h, 90%; (iii) 2-methyl-2-butene, $\text{BH}_3\text{-SMe}_2$, 0 °C, 76%; (iv) Dess-Martin periodinane, py, CH_2Cl_2 , 20 °C, 77%; (v) **17**, *n*-BuLi, LiBr, THF, -78 °C, then **16**, 84%; (vi) TPAP, NMO, 4 Å mol sieves, CH_2Cl_2 , 20 °C, 94%; (vii) H_2 , PtO_2 , K_2CO_3 , THF-MeOH (1 : 1), 94%; (viii) CSA, CH_2Cl_2 , 20 °C, 4 h, 93%; (ix) TBAF, CH_2Cl_2 , 20 °C, 3 h, 77%; (x) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3 , DEAD, 78%; (xi) *m*-CPBA, NaHCO_3 , 71%; (xii) KHMDS, THF, -78 °C then **5a**, 84%; (xiii) H_2 , PtO_2 , K_2CO_3 , THF-MeOH (1 : 1), 85%.



Scheme 3 Reagents and conditions: (i) **6** and **7** (1 : 1), KHMDS, THF, $-78\text{ }^{\circ}\text{C}$ then **5b**, 76%; (ii) H_2 , PtO_2 , K_2CO_3 , THF–MeOH (1 : 1), 90%.

Julia olefination using KHMDS proceeded in excellent yield (84%) providing a 1 : 1 mixture of phthalide-spiroacetals (3*S*,2''*S*,5''*S*,7''*S*)-(1a) and (3*S*,2''*S*,5''*R*,7''*S*)-(2a) after hydrogenation over PtO_2 .

The ^1H and ^{13}C NMR data recorded for phthalide-spiroacetals **1a** and **2a** were compared with the data reported for the natural products.⁵ Notably the chemical shifts observed for the key resonances at the stereogenic centres in the spiroacetal unit ($\text{C}2''$, $\text{C}5''$, $\text{C}7''$ and $2''\text{-Me}$) were in good agreement with the natural products (Fig. S2†). However, the chemical shift reported for H3 (δ_{H} 5.29) in both **1a** and **2a** was at variance with the chemical shift reported for the same resonance in natural CJ-12,954 and CJ-13,014 (δ_{H} 5.27). Further clarification of the relative stereochemistry between C3 on the phthalide with the stereogenic centres in the 5,5-spiroacetal ring was clearly required.

Due to the ready availability of (3*R*)-phthalide-aldehyde **5b**¹⁰ we also prepared a 1 : 1 mixture of (3*R*,2''*S*,5''*S*,7''*S*)-(1b) and (3*R*,2''*S*,5''*R*,7''*S*)-(2b) with (3*R*)-stereochemistry on the phthalide (Scheme 3) *via* olefination of (3*R*)-phthalide-aldehyde **5b** with a 1 : 1 mixture of sulfones **6** and **7** followed by hydrogenation. Frustratingly, the ^1H and ^{13}C NMR data obtained for these latter isomers were similar to those recorded for both synthetic isomers (1a) and (2a) and the respective natural products (Fig. S2†).

Gratifyingly, procurement of samples of natural CJ-12,954 and CJ-13,014 allowed direct comparison of the HPLC retention times for the synthetic compounds with the natural products. Using the reported HPLC conditions^{5§} the retention times for the 1 : 1 mixture of synthetic (3*S*,2''*S*,5''*S*,7''*S*)-(1a) and (3*S*,2''*S*,5''*R*,7''*S*)-(2a) were in agreement with those recorded for natural CJ-12,954 (1) and CJ-13,014 (2), and differed from the retention times recorded for the 1 : 1 mixture of synthetic (3*R*,2''*S*,5''*S*,7''*S*)-(1b) and (3*R*,2''*S*,5''*R*,7''*S*)-(2b). The $[\alpha]_{\text{D}} -38.0$ (c , 0.48, CHCl_3) for the 1 : 1 mixture of (3*S*,2''*S*,5''*S*,7''*S*)-(1a) and (3*S*,2''*S*,5''*R*,7''*S*)-(2a) was of opposite sign and an average of the values reported⁵ for CJ-12,954 (1), $[\alpha]_{\text{D}} +6.0$ (c , 0.07, CHCl_3), and CJ-13,014 (2), $[\alpha]_{\text{D}} +71.2$ (c , 0.11, CHCl_3), establishing that the synthetic isomers (3*S*,2''*S*,5''*S*,7''*S*)-(1a) and (3*S*,2''*S*,5''*R*,7''*S*)-(2a) were in fact enantiomeric to the natural products.

In summary, the first synthesis of the enantiomers of the helicobactericidal agents CJ-12,954 and CJ-13,014, namely (3*S*,2''*S*,5''*S*,7''*S*)-(1a) and (3*S*,2''*S*,5''*R*,7''*S*)-(2a), has been achieved *via* modified Julia olefination of (3*S*)-phthalide-aldehyde **5a** with a 1 : 1 mixture of heterocyclic sulfones **6** and **7**. Complementary synthesis of the diastereomers (3*R*,2''*S*,5''*S*,7''*S*)-(1b) and (3*R*,2''*S*,5''*R*,7''*S*)-(2b) facilitated confirmation of the relative stereochemistry between C-3 on the phthalide unit and $\text{C}5''/\text{C}7''$ on the 5,5-spiroacetal moiety, establishing that the absolute configuration of the natural product CJ-12,954 is (3*R*,2''*R*,5''*R*,7''*R*) and that of CJ-13,014 is (3*R*,2''*R*,5''*S*,7''*R*).

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Notes and references

‡ HPLC conditions: Chiracel[®] OD-H column, *i*-propanol : hexane 5 : 95, flow rate 0.5 mL min^{-1} , retention times: 7.5 min (minor, *R*-isomer) and 8.7 min (major, *S*-isomer).

§ HPLC conditions: YMC-Pack ODS-AM column, methanol : water 3 : 1, flow rate 0.5 mL min^{-1} .

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