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

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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 ^{1}H and ^{13}C 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 epithelium[1] 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-compliance[4] 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, spirolaxine **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′-CH_2 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′-CH_2 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 reported[10] the synthesis of (+)-spirolaxine 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 (+)-spirolaxine 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-oxazaborolidine[13] and borane–dimethyl sulfide affording homoallylic alcohol **9** in 92% yield and 94% e.e.[14]

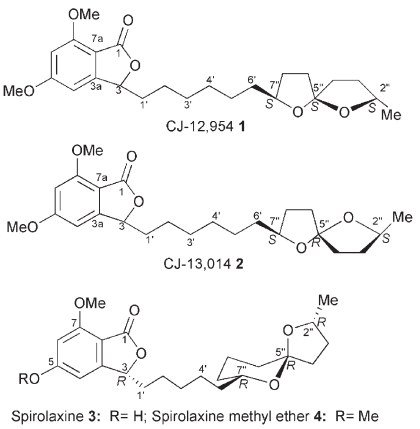

Fig. 1

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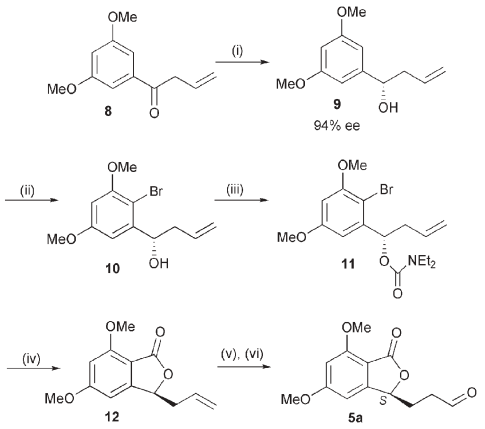
† Electronic supplementary information (ESI) available: Experimental section and Fig. S2 depicting key NMR data for **1a/2a** and **1b/2b**. See DOI: 10.1039/b612757f



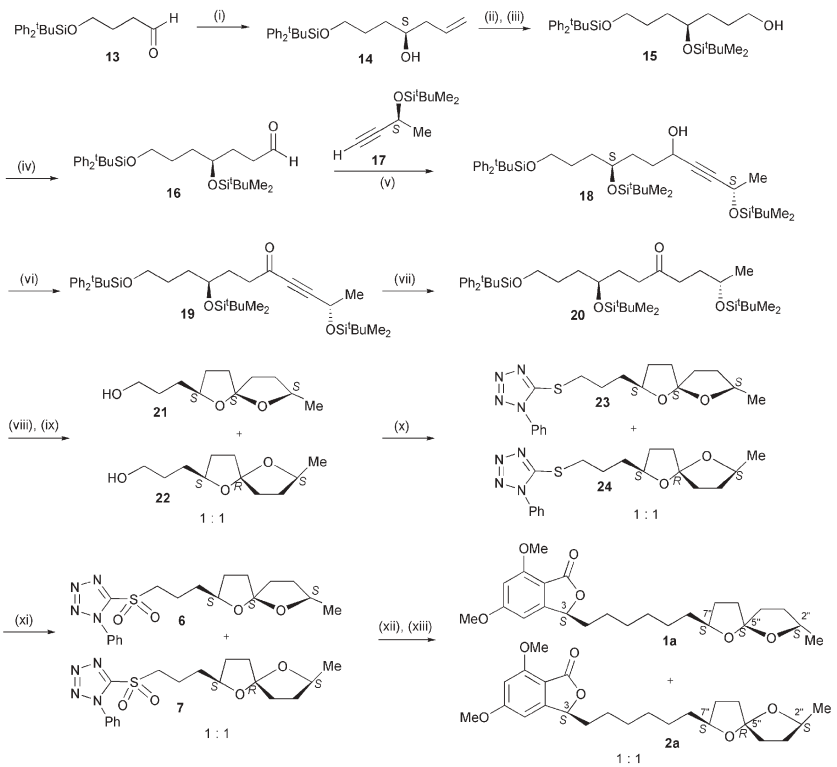
Scheme 1 *Reagents and conditions*: (i) (*R*)-MeCBS, BH_3–SMe_2, 15 min, then THF, **8**, 2 h, 92%, 94% ee; (ii) NBS, NH_4OAc, Et_2O, 24 h, 90%; (iii) NaH, THF, 0 °C then *N*,*N*-diethylcarbamoyl chloride, 90%; (iv) *t*-BuLi, THF, −78 °C, 2 h then camphorsulfonic acid, 20 °C, 12 h, 70%; (v) 2-methyl-2-butene, BH_3–SMe_2, THF, 0 °C then MeOH, NaOH, 30% H_2O_2, 71%; (vi) TPAP, NMO, CH_2Cl_2, 4Å 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]

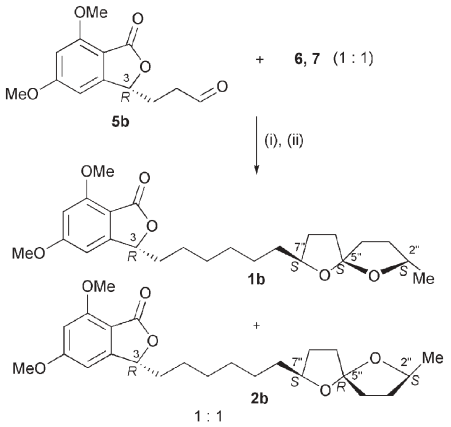
Attention next focused on the synthesis of sulfones **6** and **7** which are epimeric at the spirocentre (Scheme 2). 1-Phenyl-1*H*-tetrazol-5-yl sulfones **6** and **7** were chosen in preference to the use of benzothiazol-2-yl sulfones due to their increased stability in heterocycle-modified Julia 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 bromide[20] 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 effect[21] 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-activated[15] modified



Scheme 2 *Reagents and conditions*: (i) allyl bromide, Mg, (+)-β-diisopinocampheylmethoxyborane, Et_2O, −78 °C to 20 °C, 82%, 94% ee; (ii) *t*-$BuMe_2SiCl$, imidazole, DMAP, CH_2Cl_2, 20 °C, 12 h, 90%; (iii) 2-methyl-2-butene, BH_3–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, 4Å 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-1H-tetrazole-5-thiol, Ph_3P, 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 °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 ^{1}H 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 (C2″, C5″, C7″ and 2″-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 ^{1}H 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 $[\alpha]_D$ −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 reported[5] for CJ-12,954 (**1**), $[\alpha]_D$ +6.0 (*c*, 0.07, $CHCl_3$), and CJ-13,014 (**2**), $[\alpha]_D$ +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 C5″/C7″ 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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