Synthesis and assignment of the absolute configuration of the anti-*Helicobacter pylori* agents CJ-12,954 and CJ-13,014†

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The synthesis of the spiroacetal-containing anti-*Helicobacter pylori* agents (3*S*,2″*S*,5″*S*,7″*S*)-**1a** (*ent*-CJ-12,954) and (3*S*,2″*S*,5″*R*,7″*S*)-**2a** (*ent*-CJ-13,014) has been carried out based on the convergent union of a 1 : 1 mixture of heterocycle-activated spiroacetal sulfones **6** and **7** with (3*S*)-phthalide aldehyde **5a**. The synthesis of the (3*R*)-diastereomers (3*R*,2″*S*,5″*S*,7″*S*)-**1b** and (3*R*,2″*S*,5″*R*,7″*S*)-**2b** was also undertaken in a similar manner by union of (3*R*)-phthalide aldehyde **5b** with a 1 : 1 mixture of spiroacetal sulfones **6** and **7**. 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. The (2*S*,8*S*)-stereochemistry in protected dihydroxyketone **21**, the precursor to the mixture of spiroacetal sulfones **6** and **7** was established *via* union of readily available (*S*)-acetylene **18** with aldehyde **17** in which the (4*S*)-stereochemistry was established *via* asymmetric allylation. Deprotection and cyclization of protected dihydroxyketone **21** afforded an inseparable 1 : 1 mixture of spiroacetal alcohols **24** and **25** that were converted into a 1 : 1 inseparable mixture of spiroacetal sulfones **6** and **7**. Phthalide-aldehyde **3a** was prepared *via* intramolecular acylation of bromocarbamate **11** in which the (3*S*)-stereochemistry was established *via* asymmetric CBS reduction of ketone **8**.

Introduction

Helicobacter pylori are microaerophilic, Gram negative bacteria[1] which colonize the stomach of over half the world's population[2] and have an etiological role in several diseases including gastric and duodenal ulcers, distal gastric cancer and MALT lymphoma.[3] In most cases infection will persist for the lifetime of an individual without medical intervention.[4] A variety of effective drugs for the treatment and eradication of *Helicobacter pylori* infection are clinically useful including antibiotics (β-lactams, macrolides and quinolones), bactericidal agents (bismuth salts) and anti-protozoal agents (metronidazole); however, drug resistance, side effects and non-compliance are common problems in the use of such drugs.[5] Current treatment of *Helicobacter pylori* infection involves the prescription of one or more antibiotics in combination with H_2 blockers; however, none of the existing treatments are capable of complete eradication of *Helicobacter pylori*.[6] Consequently, there is an urgent need for the development of more effective and selective anti-*Helicobacter pylori* agents.

In a screening program designed to discover such compounds, Dekker *et al.*[7] isolated seven new 5,7-dimethoxyphthalide antibiotics with specific anti-*Helicobacter 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 has 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**, produced by various strains of white rot fungi belonging to the genera *Sporotrichum* and *Phanerochaete*, contain a 6,5-spiroacetal ring joined through a polymethylene

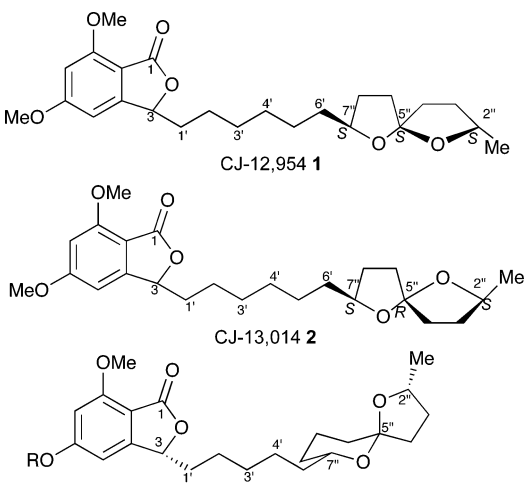

Fig. 1 Structures of anti-*Helicobacter pylori* agents.

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† Electronic supplementary information (ESI) available: General experimental details together with full experimental procedures, ^{1}H NMR, ^{13}C NMR and mass spectral data for compounds **5a**, **8–21**, **30** and **31**. See DOI: 10.1039/b709932k

chain to a phthalide unit.[8] Thus, phthalide-containing spiroacetal compounds provide promising new leads for the treatment of *Helicobacter pylori* related diseases.

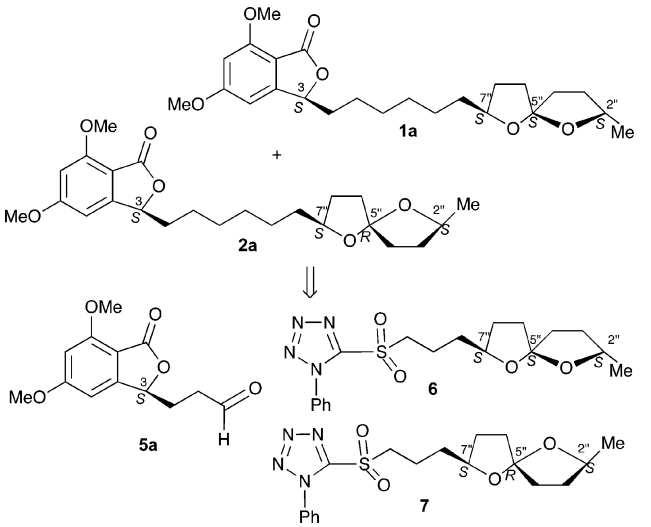
Whilst Dekker *et al.*[7] were unable to assign the stereochemistry of the stereogenic centre at C-3 on the phthalide unit in CJ-12,954 **1** and CJ-13,014 **2**, they were able to assign the relative stereochemistry of the three stereogenic centres on the spiroacetal ring. CJ-12,954 **1** was assigned 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 in the spiroacetal ring and at C-3 on the phthalide unit is reliant on the execution of a total synthesis of these natural products.

Whilst a synthesis of the phthalide-spiroacetals CJ-12,954 **1** and CJ-13,014 **2** has not been reported to date, several of the simpler non spiroacetal-containing phthalides have been prepared with lack of stereocontrol of the phthalide unit.[9–11] We have previously reported[12] the first enantioselective total synthesis of (+)-spirolaxine methyl ether **4** that established the absolute configuration of the natural product to be (3*R*,2″*R*,5″*R*,7″*R*). This conclusion was later confirmed by single-crystal X-ray analysis[13] of spirolaxine **3** and an independent synthesis of spirolaxine methyl ether **4**.[14] We now herein report the full details[15] of our synthesis of the anti-*Helicobacter pylori* agents (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** thereby establishing that the synthetic isomers **1a** and **2a** were in fact enantiomeric to the natural products CJ-12,954 and CJ-13,014.

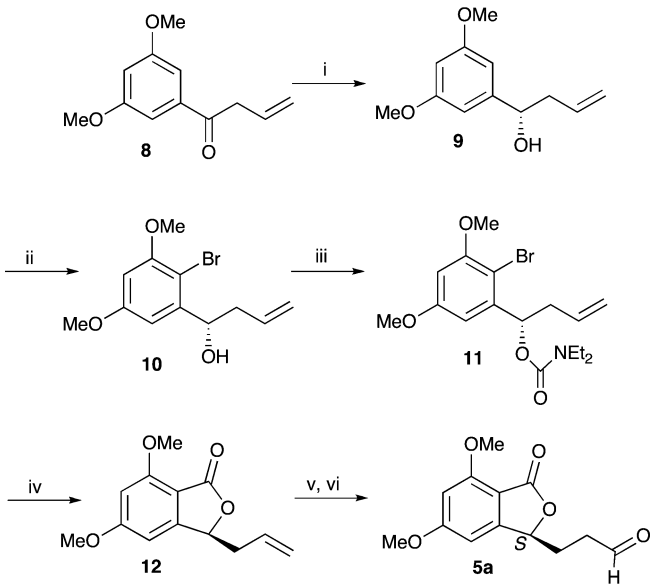
Results and discussion

Given that the absolute stereochemistry of the four stereogenic centres in CJ-12,954 **1** and CJ-13,014 **2** had not been assigned, it was important to develop a flexible modular approach that would allow variation in the construction of the stereogenic centres in these molecules. Our attention initially focused 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 an (*S*)-configuration at C-3 on the phthalide unit and an (*S*)-configuration at both C-2″ and C-7″ on the spiroacetal unit (Scheme 1). It was envisaged that control of the stereochemistry of the spirocentre in the 5,5-spiroacetal ring system would be more difficult hence our efforts were directed to the synthesis of a 1 : 1 mixture of heterocycle-activated sulfones **6** and **7** in preparation for union with (3*S*)-phthalide-aldehyde **5a** using a modified Julia–Kocienski olefination.

The synthesis of (3*S*)-phthalide-aldehyde **5a** hinged on the initial synthesis of (*S*)-alcohol **9** that undergoes regioselective bromination to bromide **10** and conversion to bromocarbamate **11** (Scheme 2). Carbamate **11** is then transformed into phthalide-aldehyde **5a** *via* intramolecular acylation and hydroboration–oxidation of the olefin. Whilst the efficacy of the latter steps had been readily demonstrated[12] in the enantiomeric series to prepare (3*R*)-phthalide-aldehyde **5b** the synthesis of (*S*)-alcohol **9** in high enantiopurity needed attention. For the synthesis of (3*R*)-phthalide-aldehyde **5b** the (*R*)-enantiomer of alcohol **9** was established *via* asymmetric allylation of 3,5-dimethoxybenzaldehyde for which the optimal enantiomeric excess (ee) obtained was only 86%. We therefore decided to investigate an asymmetric reduction procedure to prepare (*S*)-alcohol **9** in the present work.



Scheme 1 Retrosynthesis of (3*S*,2″*S*,5″*S*,7″*S*)-**1a** and (3*S*,2″*S*,5″*R*,7″*S*)-**2a**.



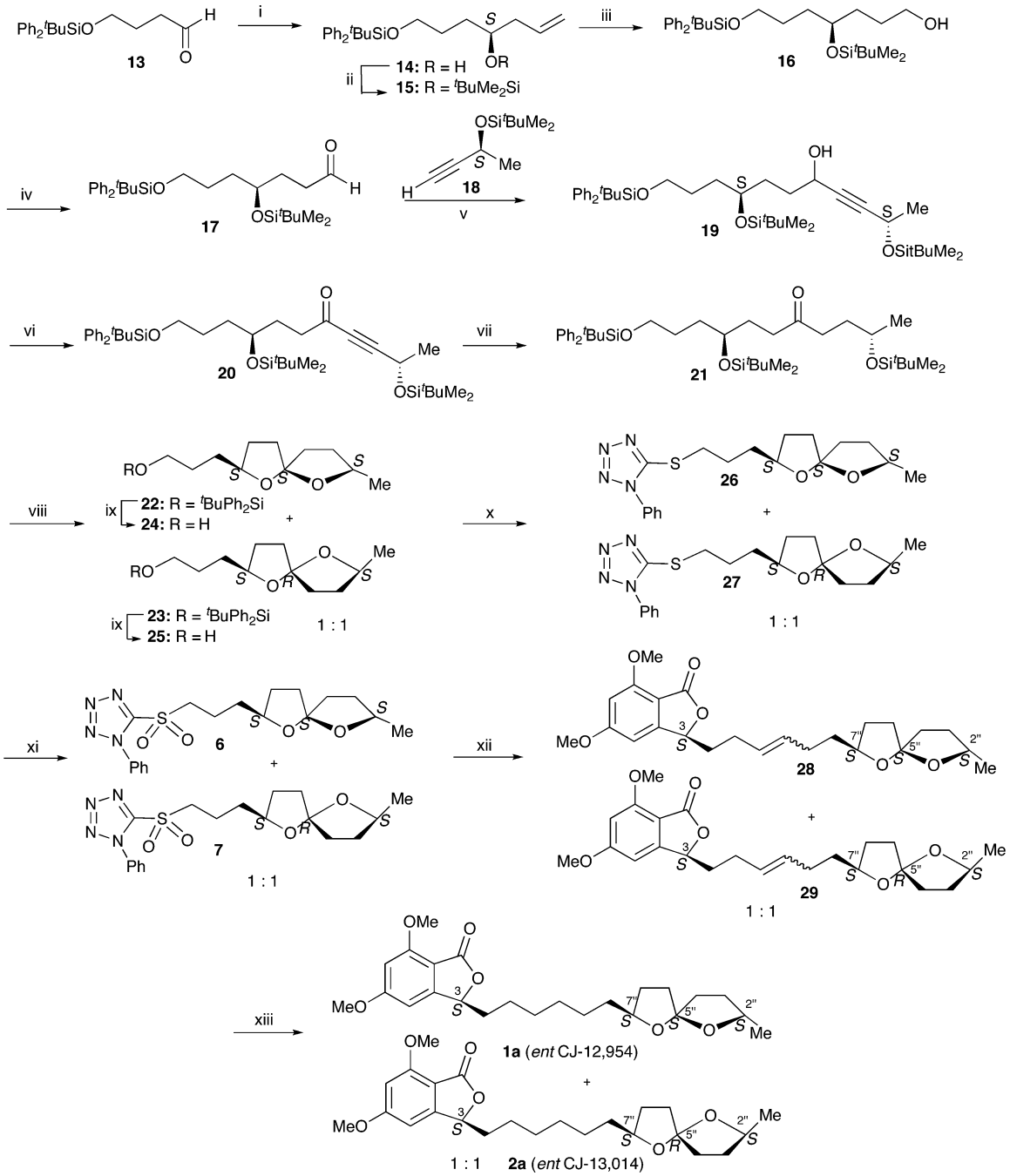
Scheme 2 *Reagents and conditions*: (i) (*R*)-Me-CBS-oxazaborolidine (CBS = Corey–Bakshi–Shibata), BH_3–SMe_2, 15 min, then THF, **8**, 2 h, 92%, 94% ee; (ii) NBS, NH_4OAc, Et_2O, 24 h, 90%; (iii) NaH, THF, 0 °C then *N*,*N*-diethylcarbamoyl chloride, 90%; (iv) *t*-BuLi, THF, −78 °C, 2 h then camphorsulfonic 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, 4 Å mol. sieves, 6 h, 20 °C, 72%.

Asymmetric reduction of ketone **8** using (−)–DIP-Cl in THF at −35 °C following the procedure reported by Wang *et al.*[16] afforded (*S*)-alcohol **9** in only 40% yield with 92% ee. Fortunately, reduction of ketone **8** with (*R*)-2-methyl-CBS-oxazaborolidine[17] (1.0 equiv.) and borane–dimethyl sulfide (1.0 equiv.) in THF at −20 °C for 2 h afforded (*S*)-alcohol **9** in higher 92% yield with an improved 94%

ee as determined by conversion to a Mosher ester derivative. It was noted that if an excess of borane–dimethyl sulfide relative to (*R*)-2-methyl-CBS-oxazaborolidine was used then rearrangement of the β,γ-unsaturated ketone to the more stable α,β-unsaturated ketone occurred with none of the desired alcohol **9** being formed.

With a facile synthesis of (*S*)-alcohol **9** in hand, conversion to (3*S*)-phthalide-aldehyde **5a** proceeded uneventfully *via* bromination to bromide **10**, formation of carbamate **11** using sodium hydride and *N*,*N*-diethylcarbamoyl chloride followed by internal acylation of the derived *ortho*-lithiated species formed upon halogen–metal exchange to afford phthalide **12**. Hydroboration of the olefin and subsequent oxidation using tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide secured (3*S*)-phthalide-aldehyde **5a**.[11]

Our attention next focused on the synthesis of 1-phenyl-1*H*-tetrazol-5-yl spiroacetal sulfones **6** and **7** that are epimeric at the spirocentre with an (*S*)-configuration at C-2″ and C-7″ (Scheme 3). The synthesis of (2*S*,5*S*,7*S*)-spiroacetal **6** and



Scheme 3 *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, $BH_3{\cdot}SMe_2$, 0 °C, 76%; (iv) Dess–Martin periodinane, py, CH_2Cl_2, 20 °C, 77%; (v) 18, *n*-BuLi, LiBr, THF, −78 °C, then **17**, 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, 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%.

(2*S*,5*R*,7*S*)-spiroacetal **7** was arbitrarily pursued due the ready availability of 3-butyn-1-ol **18**[18] with (*S*)-absolute stereochemistry that upon conversion to the corresponding lithium (*S*)-acetylide leads to the 5,5-spiroacetal ring system with (*S*)-stereochemistry at C-2″. The corresponding (*S*)-stereochemistry at C-7″ in the 5,5-spiroacetal ring system is derived from homoallylic alcohol **14** that is available *via* asymmetric allylation of aldehyde **13**. Importantly, 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.[19,20]

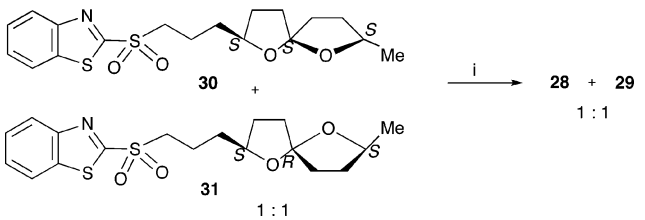
Addition of allylmagnesium bromide to (+)-β-diisopinocampheylmethoxyborane in diethyl ether at −78 °C followed by addition to aldehyde **13**[21] afforded (*S*)-alcohol 14 in 82% yield after peroxide work-up for which the ee was determined to be 94% by chiral HPLC. (*S*)-Alcohol **14** has previously been prepared by an alternative procedure however the ee was not determined in this case.[22] The (*R*)-enantiomer of alcohol **14** has also been prepared previously in 74% ee using a tartaric acid derived allylboration.[23] Gratifyingly, the asymmetric reduction method reported herein offers a significant improvement on existing methods to prepare this compound enantioselectively. Protection of the alcohol as a *tert*-butyldimethylsilyl ether **15** followed by hydroboration to primary alcohol **16** the oxidation using Dess–Martin periodinane afforded aldehyde **17**.

Addition of aldehyde **17** to the lithium acetylide of **18** at −78 °C and at −100 °C initially proved problematic with only low yields of the desired alcohol **19** being obtained. Due to the continual recovery of starting materials along with the coupled product **19** it was postulated that enolate formation was occurring in preference to the desired nucleophilic addition reaction. Brandsma *et al.*[24] and Carreira *et al.*[25] have incorporated the use of lithium bromide to prevent a similar problem in the reaction of lithium acetylides with ketones. In the present case reaction of aldehyde **17** with the lithium acetylide of **18** in tetrahydrofuran at −78 °C, with the inclusion of 50 mol% of lithium bromide, proceeded cleanly furnishing alcohol **19** as a mixture of diastereomers in 84% yield.

Oxidation of the alcohol **19** to ynone **20** using tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide followed by reduction of the acetylene over Adams's catalyst (PtO_2) afforded saturated protected dihydroxyketone **21**. Spirocyclization was then readily effected in 93% yield using camphorsulfonic acid in dichloromethane affording an inseparable 1 : 1 mixture of spiroacetals **22** and **23** that were converted into spiroacetal alcohols **24** and **25** after cleavage of the *tert*-butyldiphenylsilyl ether with tetrabutylammonium fluoride. Lack of stereocontrol from the anomeric effect and/or steric effects contributed to the observed formation of equal quantities of 5,5-spiroacetals **24** and **25** with (*S*)- and (*R*)-stereochemistry at the spirocentres, respectively. For spirocyclizations involving two five-membered rings a strong anomeric effect was not expected due to lack of well-defined axial or equatorial positions in these systems.[26]

In the ^{1}H NMR spectrum for the mixture of spiroacetals **24** and **25**, resonances at δ 4.05 (dddd, *J* 10.7, 8,7, 4.9, 2.2 Hz) and δ 4.19 (qdd, *J* 6.4, 6.4, 2.2 Hz), corresponding to H7 and H2 respectively, displayed multiplicities that were indicative of cyclic ring formation. Two doublets at δ 1.21 and δ 1.30 (*J* 6.2 Hz) of equal intensity, were assigned to the individual methyl groups of each spiroacetal alcohol. Further support for the successful formation of spiroacetal alcohols **24** and **25** was the observation of two quaternary carbon resonances in the ^{13}C NMR spectrum at δ 114.3 and δ 114.7 which were characteristic of 5,5 spiroacetal carbons. A molecular ion at *m*/*z* 201.1490 in the high resolution CI mass spectrum (201.1491 calculated for MH^+) provided further evidence for the successful formation of the spiroacetal alcohols **24** and **25**.

With phthalide-aldehyde **5a** and spiroacetal alcohols **24** and **25** in hand, attention turned to their union to form the carbon skeleton of CJ-12,952 and CJ-13,014. Use of benzothiazol-2-yl sulfones **30** and **31** as coupling partners for the modified Julia–Kocienski olefination proved disappointing with only low yields of the desired coupled olefins **28** and **29** being obtained (Scheme 4). The low yield obtained in the reaction was attributed to the instability of the benzothiazol-2-yl sulfone. The self-condensation of the benzothiazol-2-yl sulfones has been well documented in the literature[27] hence we turned our efforts to the use of the more stable 1-phenyl-1*H*-tetrazol-5-yl sulfones developed by Kocienski *et al.*[20] There are no literature reports on the use of a spiroacetal-containing 1-phenyl-1*H*-tetrazol-5-yl sulfone in a modified Julia olefination. However, Bondar and Paquette[28] have reported the addition of a 1-phenyl-1*H*-tetrazol-5-yl sulfone to a spiroacetal-containing aldehyde in their synthetic studies towards pectenotoxin-2.



Scheme 4 *Reagents and conditions*: (i) KHMDS, THF, −78 °C then **5a**, −78 °C, 1.1 h, warm to room temp., 1 h, 19%.

Triphenylphosphine, 1-phenyl-1*H*-tetrazol-5-thiol, and diethyl azodicarboxylate were added to a solution of spiroacetal alcohols **24** and **25** in tetrahydrofuran at 0 °C, then stirred at room temperature for 15 h to yield sulfides **26** and **27** (Scheme 3). Sulfides **26** and **27** were then treated with *m*-chloroperoxybenzoic acid and sodium bicarbonate in dichloromethane at room temperature for 24 h to afford sulfones **6** and **7** in excellent yield.

Attention next focused on the union of sulfones **6** and **7** with (3*S*)-phthalide-aldehyde **5a** (Scheme 3). Potassium hexamethyldisilazide was added to a solution of sulfones **6** and **7** in tetrahydrofuran at −78 °C and the mixture stirred for 20 min. (3*S*)-Phthalide-aldehyde **5a** was then added and the mixture stirred for 90 min at −78 °C, then warmed to room temperature for 1 h to afford a mixture of alkenes **28** and **29** in 84% yield. The ratio of (*E*)- and (*Z*)-alkenes **28** and **29** obtained from this reaction was not determined. Finally hydrogenation of the mixture of alkenes **28** and **29** over Adams' catalyst (PtO_2) in tetrahydrofuran–methanol (1 : 1) in the presence of potassium carbonate at room temperature for 4 h afforded an inseparable 1 : 1 mixture of (3*S*,2″*S*,5″*S*,7″*S*)-**1a** and (3*S*,2″*S*,5″*R*,7″*S*)-**2a** in 85% yield after purification by flash chromatography.

Characteristic resonances at δ 114.3 and 114.7 assigned to C5″ in (3*S*,2″*S*,5″*S*,7″*S*)-**1a** and (3*S*,2″*S*,5″*R*,7″*S*)-**2a**, respectively, supported the presence of the 5,5-spiroacetal ring system. The

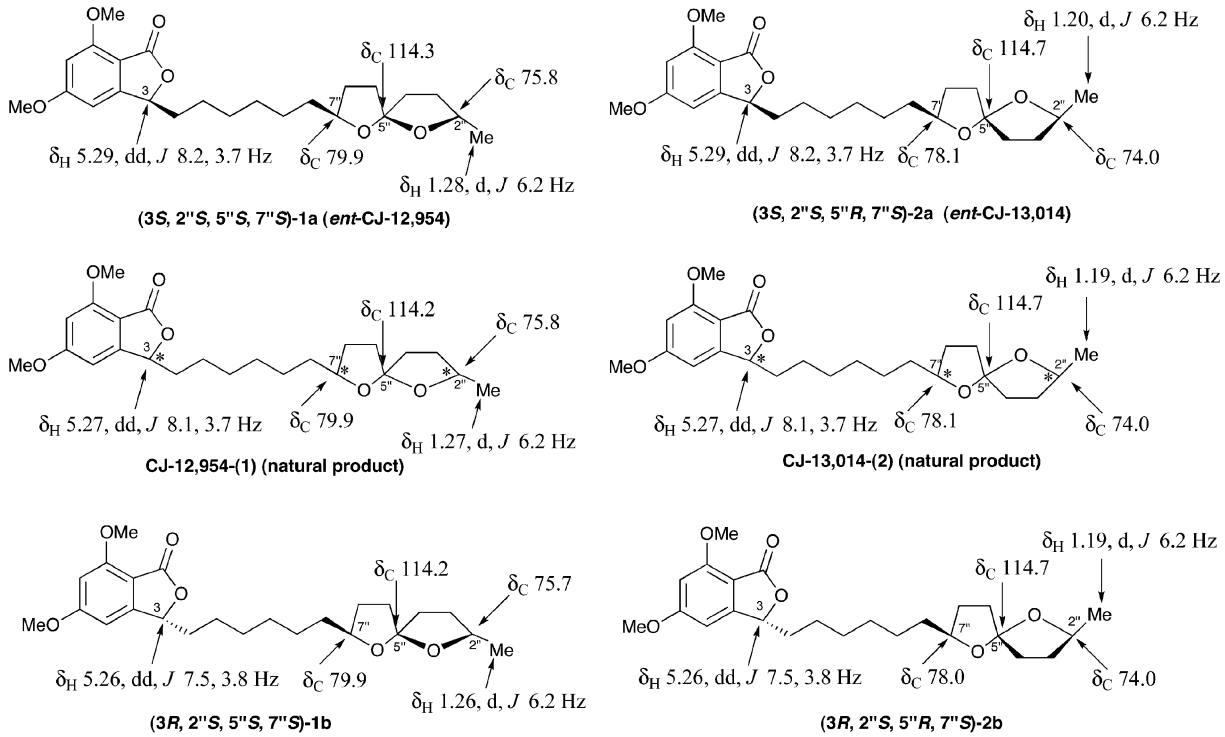


Fig. 2

^{1}H NMR spectrum displayed two doublets at δ 1.20 and 1.28 ppm (J 6.2 Hz) assigned to the methyl group in (3*S*,2″*S*,5″*R*,7″*S*)-**2a** and (3*S*,2″*S*,5″*S*,7″*S*)-**1a**, respectively, in good agreement with the data for the natural products (Fig. 2). A doublet of doublets at δ 5.29 ppm (J 8.2, 3.7 Hz) was assigned to H3 in the phthalide moiety with the chemical shift at variance with the chemical shift reported for the same resonance at δ 5.27 (dd, J 8.1, 3.7 Hz) in the natural products CJ-12,954 **1** and CJ-13,014 **2**.[7]

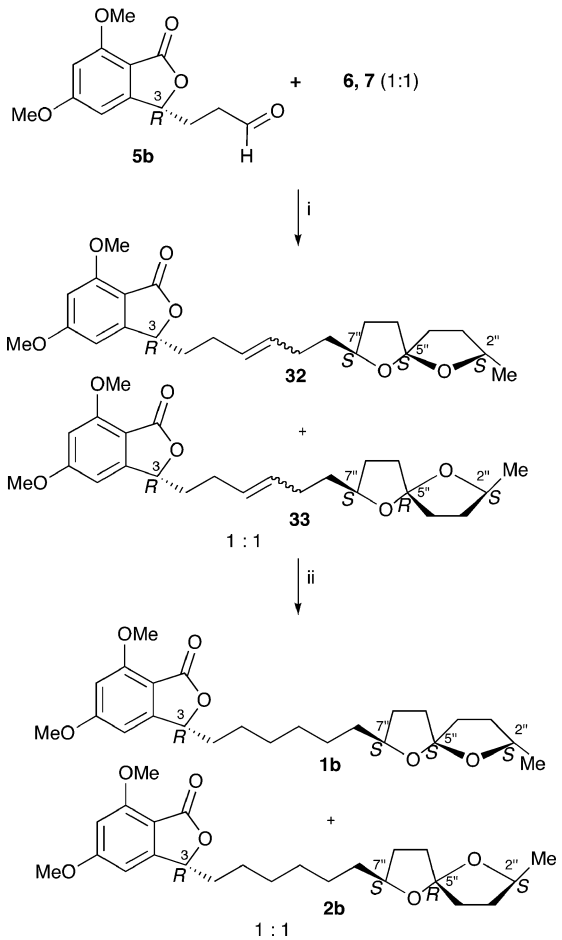
Due the ready availability of (3*R*)-phthalide-aldehyde **5b** within our research group[12] we also prepared the closely related phthalide-spiroacetals **1b** and **2b** with (3*R*)-stereochemistry on the phthalide (Scheme 5). Thus, olefination of (3*R*)-phthalide-aldehyde **5b** with a 1 : 1 mixture of sulfones **6** and **7** followed by hydrogenation of the resultant olefins **32** and **33** afforded a 1 : 1 mixture of (3*R*,2″*S*,5″*S*,7″*S*)-**1b** and (3*R*,2″*S*,5″*R*,7″*S*)-**2b**. Frustratingly, the ^{1}H and ^{13}C NMR data obtained for these latter isomers was similar to that recorded for both synthetic isomers **1a** and **2a** and the respective natural products (Fig. 2).

Unfortunately, separation of (3*S*,2″*S*,5″*S*,7″*S*)-**1a** and (3*S*,2″*S*,5″*R*,7″*S*)-**2a** from each other, and (3*R*,2″*S*,5″*S*,7″*S*)-**1b** and (3*R*,2″*S*,5″*R*,7″*S*)-**2b** from each other proved exceedingly difficult. Use of column chromatography, thin layer chromatography and normal phase HPLC did not facilitate separation of the individual diastereomers. A small sample of pure (3*R*,2″*S*,5″*R*,7″*S*)-**2b** was successfully isolated after repeated use of flash column chromatography, however, no other diastereomer was able to be completely separated from its corresponding 5″-epimer.

The key ^{1}H NMR and ^{13}C NMR data observed for (3*S*,2″*S*,5″*S*,7″*S*)-**1a** and (3*R*,2″*S*,5″*S*,7″*S*)-**1b** proved to be very similar to that obtained by Dekker *et al.*[7] for the natural product CJ-12,954 **1**. (Fig. 2). For example, the methyl group on the spiroacetal ring in the natural product CJ-12,954 **1** resonated at δ_H 1.27 ppm (d, J 6.2 Hz) in the ^{1}H NMR spectrum and δ_C 23.0 ppm in the ^{13}C NMR spectrum. For (3*S*,2″*S*,5″*S*,7″*S*)-**1a** the methyl group resonated at δ_H 1.28 ppm (d, J 6.2 Hz) and δ_C 23.0 ppm, whilst in (3*R*,2″*S*,5″*S*,7″*S*)-**1b** the methyl group resonated at δ_H 1.26 ppm (d, J 6.2 Hz) in the ^{1}H NMR spectrum and at δ_C 22.9 ppm in the ^{13}C NMR spectrum.

Likewise, the key ^{1}H NMR and ^{13}C NMR data for (3*S*,2″*S*,5″*R*,7″*S*)-**2a** and (3*R*,2″*S*,5″*R*,7″*S*)-**2b** was almost identical to the data reported by Dekker *et al.*[7] for the natural product CJ-13,014 **2**. (Fig. 2). For example, the methyl group on the spiroacetal in the natural product CJ-13,014 **2** resonated at δ_H 1.19 ppm (d, J 6.2 Hz) in the ^{1}H NMR spectrum and at δ_C 21.1 ppm in the ^{13}C NMR spectrum. For (3*S*,2″*S*,5″*R*,7″*S*)-**2a** the methyl group resonated at δ_H 1.20 ppm (d, J 6.2 Hz) in the ^{1}H NMR spectrum and at δ_C 21.1 ppm in the ^{13}C NMR spectrum, and for (3*R*,2″*S*,5″*R*,7″*S*)-**2b** the methyl group resonated at δ_H 1.21 ppm (d, J 6.2 Hz) in the ^{1}H NMR spectrum and at δ_C 21.1 ppm in the ^{13}C NMR spectrum.

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**, and 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**, were analysed by HPLC, using the same conditions (YMC-Pack ODS-AM column, methanol : water (3 : 1), flow rate 0.5 mL min^{-1}) reported by Dekker *et al.*[7] for the separation of the natural products CJ-12,954 **1** and CJ-13,014 **2**. Pure samples of the natural products CJ-12,954 **1** and CJ-13,014 **2**, obtained from Pfizer Inc., were also analysed under the same HPLC conditions. The retention time for the natural product CJ-12,954 **1** was 8.7 min, and the



Scheme 5 *Reagents and conditions*: (i) KHMDS, THF, −78 °C then **5b**, 76%; (ii) H_2, PtO_2, K_2CO_3, THF–MeOH (1 : 1), 90%.

retention time for the natural product CJ-13,014 **2** was 9.4 min. 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 8.7 and 9.4 min, respectively. The retention times 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** were 9.2 and 9.6 min. Thus, the retention times observed for the natural CJ-12,954 **1** and CJ-13,014 **2** were identical to the retention times for the synthetic mixture of (3*S*,2″*S*,5″*S*,7″*S*)-**1a** and (3*S*,2″*S*,5″*R*,7″*S*)-**2a**. Additionally, the ^{1}H and ^{13}C NMR data is very similar for natural CJ-12,954 **1** and synthetic (3*S*,2″*S*,5″*S*,7″*S*)-**1a**, and for natural CJ-13,014 **2** and synthetic (3*S*,2″*S*,5″*R*,7″*S*)-**2a**.

The optical rotation for the natural product CJ-12,954 **1** was reported in the literature as +6.0 (*c* 0.07, $CHCl_3$), whereas the optical rotation for the natural product CJ-13,014 **2** was reported as +71.2 (*c* 0.11, $CHCl_3$).[7] Due to the inability to separate (3*S*,2″*S*,5″*S*,7″*S*)-**1a** from (3*S*,2″*S*,5″*R*,7″*S*)-**2a**, the optical rotation was recorded for the 1 : 1 mixture of these two diastereomers as −38.0 (*c* 0.48, $CHCl_3$). An optical rotation of +36.4 (*c* 0.50, $CHCl_3$) was obtained for the 1 : 1 mixture of (3*R*,2″*S*,5″*S*,7″*S*)-**1b** and (3*R*,2″*S*,5″*R*,7″*S*)-**2b**. Given that the optical rotation 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** is of opposite sign and an average of the optical rotation values reported for the natural products CJ-12,954 **1** and CJ-13,014 **2**, it is therefore proposed that naturally occurring CJ-12,954 **1** exhibits (3*R*,2″*R*,5″*R*,7″*R*)-stereochemistry (*ent*-**1a**) and natural CJ-13,014 **2** exhibits (3*R*,2″*R*,5″*S*,7″*R*)-stereochemistry (*ent*-**2a**). This assignment would account for the fact that the HPLC retention times observed for synthetic (3*S*,2″*S*,5″*S*,7″*S*)-**1a** and naturally occurring CJ-12,954 **1** were identical since these compounds are in fact enantiomeric to each other. Similarly, the HPLC retention times observed for synthetic (3*S*,2″*S*,5″*R*,7″*S*)-**2a** and naturally occurring CJ-13,014 **2** are also enantiomeric.

In summary the synthesis 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* Kocienski modified Julia olefination of (3*S*)-phthalide-aldehyde **5a** with a 1 : 1 mixture of heterocyclic sulfones **6** and **7**. Further complementary synthesis of the (3*R*)-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. The synthetic work herein reported thus establishes unequivocally that the absolute configuration of the four stereogenic centres in the natural product CJ-12,954 is (3*R*,2″*R*,5″*R*,7″*R*) and in CJ-13,014 is (3*R*,2″*R*,5″*S*,7″*R*).

Experimental

(2*S*,5*R*,7*S*) and (2*S*,5*S*,7*R*)-7-(3′-(*tert*-Butyldiphenylsilyloxy)-propyl)-2-methyl-1,6-dioxaspiro[4.4]nonane (22) and (23)

To a solution of (2*S*,8*S*)-ketone **21** (50 mg, 0.07 mmol) in dichloromethane (3 mL) was added camphorsulfonic acid (35 mg, 0.15 mmol). The solution was stirred for 4 h then filtered through a plug of Celite® and the solvent removed under reduced pressure. The crude oil was purified by flash column chromatography using hexane–diethyl ether (95 : 5) as eluent to afford the *title compounds* **22** and **23** (30 mg, 93%) as a clear colourless oil and as a 1 : 1 mixture of two diastereomers; ν_{max} (film)/cm^{-1}) 2960, 2856, 1472, 1427, 1111, 1008, 822, 739, 701; δ_H (300 MHz, $CDCl_3$)‡ 1.07 (9H, s, Si^{t}BuPh_2), 1.23 (1.5H, d, *J* 6.2 Hz, Me), 1.29 (1.5H, d, *J* 6.2 Hz, Me*), 1.43–1.78 (6H, m, H3A, H8A, H2′, H3′), 1.91–2.17 (6H, m, H3B, H4, H8B, H9), 3.70 (2H, t, *J* 6.2 Hz, H3′), 4.06–4.13 (1H, m, H7), 4.20 (1H, qd, *J* 6.3, 6.3 Hz, H2), 7.37–7.45 (6H, m, Si^{t}Bu*Ph*$_2$, *m* and *p*), 7.69 (4H, dd, *J* 7.3, 1.4 Hz, Si^{t}Bu*Ph*$_2$, *o*); δ_C (75.5 MHz, $CDCl_3$) 19.2 (quat., Si^{t}BuPh_2), 21.2 (CH_3, Me‡), 23.0 (CH_3, Me$^\phi$), 26.9 (CH_3, Si^{t}BuPh_2), 29.0 (CH_2, C2′), 29.3 (CH_2, C2′*), 30.2 (CH_2, C8), 30.8 (CH_2, C8*), 32.0 (CH_2, C3), 32.2 (CH_2, C3*), 33.7 (CH_2, C1′*), 35.6 (CH_2, C4), 36.1 (CH_2, C9), 36.5 (CH_2, C9*), 63.9 (CH_2, C3′), 74.0 (CH, C2‡), 75.8 (CH, C2$^\phi$), 77.9 (CH, C7), 79.7 (CH, C7$^\phi$), 114.3 (quat., C5$^\phi$), 114.7 (quat., C5‡), 127.6 (CH, Si^{t}Bu*Ph*$_2$, *m*), 129.5 (CH, Si^{t}Bu*Ph*$_2$, *p*), 134.1 (quat., Si^{t}BuPh_2), 135.6 (CH, Si^{t}Bu*Ph*$_2$, *o*); *m*/*z* (CI, NH_3) 439 (MH^+, 100%), 421 (8), 381 (19), 183 (20), 165 (16); HRMS (CI): Found MH^+, 439.2665; $C_{27}H_{39}O_3Si$ requires 439.2669.

(2*S*,5*R*,7*S*) and (2*S*,5*S*,7*S*)-7-(3′-Hydroxypropyl)-2-methyl-1,6-dioxaspiro[4.4] nonane (24) and (25)

To a solution of silyl ethers **22** and **23** (0.31 g, 0.71 mmol) in tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride (0.37 g, 1.41 mmol) and the mixture stirred for 3 h. The solution

‡ The symbol * is used to denote either the (2*S*,5*R*,7*S*) or the (2*S*,5*S*,7*S*) isomer. The symbol ‡ is used to denote the (2*S*,5*R*,7*S*) isomer. The symbol $^\phi$ is used to denote the (2*S*,5*S*,7*S*) isomer.

was diluted with diethyl ether (10 mL) then saturated aqueous sodium bicarbonate (10 mL) was added. The layers were separated and the aqueous layer extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over potassium carbonate and the solvent removed under reduced pressure. The mixture was purified by flash column chromatography using hexane–diethyl ether (9 : 1–1 : 1) as eluent to yield the *title compounds* **24** and **25** (0.11 g, 0.55 mmol) as a clear colourless oil and as a 1 : 1 mixture of two diastereomers; ν_{max} (film)/cm^{-1}) 3429, 2931, 2858, 1645, 1472, 1428, 1331, 1008, 905, 823, 739, 702; δ_H (300 MHz, $CDCl_3$)‡ 1.21 (1.5H, d, *J* 6.2 Hz, Me), 1.30 (1.5H, d, *J* 6.2 Hz, Me*), 1.22–1.28 (1H, m, H8A), 1.57–1.72 (7H, m, H1′, H2′, H3, H8B), 1.97–2.31 (4H, m, H4, H9), 3.66 (2H, t, *J* 6.0 Hz, H3′), 4.05 (1H, dddd, *J* 10.7, 8,7, 4.9, 2.2 Hz, H7), 4.19 (1H, qdd, *J* 6.4, 6.4, 2.2 Hz, H2); δ_C (75.5 MHz, $CDCl_3$) 21.1 (CH_3, Me‡), 22.5 (CH_3, Me$^{\phi}$), 29.7 (CH_2, C2′), 30.4 (CH_2, C8), 32.1 (CH_2, C3), 32.7 (CH_2, C1′), 35.4 (CH_2, C4), 35.6 (CH_2, C4*), 36.1 (CH_2, C9), 36.5 (CH_2, C9*), 63.0 (CH_2, C3′), 74.2 (CH, C2‡), 76.0 (CH, C2$^{\phi}$), 78.0 (CH, C7‡), 80.0 (CH, C7$^{\phi}$), 114.3 (quat., C5$^{\phi}$), 114.7 (quat., C5‡); *m*/*z* (CI, NH_3) 201 (MH^+, 100%), 183 (56), 141 (29), 127 (6), 112 (7), 111 (6), 98 (4); HRMS (CI): Found MH^+, 201.1490; $C_{11}H_{21}O_3$ requires 201.1491.

(2″*S*,5″*R*,7″*S*) and (2″*S*,5″*S*,7″*S*)-5-(3′-(2″-Methyl-1″,6″-dioxaspiro[4.4]non-7″-yl)-propylsulfanyl)-1-phenyl-1*H*-tetrazole (26) and (27)

To a stirred solution of alcohols **24** and **25** (1 : 1 mixture) (0.22 g, 0.55 mmol) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen at room temperature was added triphenylphosphine (0.16 g, 0.61 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (0.11 g, 0.61 mmol). The mixture was cooled to 0 °C and a solution of diethyl azodicarboxylate (0.10 mL, 0.51 mmol) in tetrahydrofuran (1 mL) added dropwise *via* syringe. The solution was warmed to room temperature over 15 h then the solvent removed at reduced pressure. The residue was treated with a solution of hexane–ethyl acetate (5 : 1, v/v, 5 mL). The resultant precipitate was removed by filtration and the precipitate washed twice with hexane–ethyl acetate (5 : 1, v/v, 10 mL). The solvent was removed under reduced pressure and the resultant residue purified by flash column chromatography using hexane–diethyl ether (9 : 1) to yield the *title compounds* **26** and **27** (0.15 g, 78%) as a pale yellow oil and as a 1 : 1 mixture of diastereomers; ν_{max} (film)/cm^{-1}) 2972, 2945, 2871, 2242, 1597, 1500, 1458, 1387, 1243, 1073, 1058, 1014, 910, 761; δ_H (300 MHz, $CDCl_3$)‡ 1.14 (1.5H, d, *J* 6.2 Hz, Me‡), 1.19 (1.5H, d, *J* 6.2 Hz, Me$^{\phi}$), 1.34–1.44 (2H, m, H3″A, H8″A), 1.57–1.67 (2H, m, H3′), 1.80–1.87 (2H, m, H2′), 1.89–2.03 (6H, m, H3″B, H4″, H8″B, H9″), 3.38 (2H, t, *J* 7.0 Hz, H1′), 3.90–3.94 (0.5H, m, H7″$^{\phi}$), 3.99–4.06 (0.5H, m, H7″‡), 4.11–4.24 (1H, m, H2″), 7.48–7.51 (5H, m, Ph, *o*, *m*, *p*); δ_C (75.5 MHz, $CDCl_3$)‡ 20.9 (CH_3, Me‡), 22.8 (CH_3, Me$^{\phi}$), 25.5 (CH_2, C2′), 25.7 (CH_2, C2′*), 30.1 (CH_2, C8″), 30.5 (CH_2, C8″*), 32.0 (CH_2, C3″), 32.4 (CH_2, C3″*), 33.2 (CH_2, C1′), 34.2 (CH_2, C3′), 35.2 (CH_2, C4″), 35.4 (CH_2, C4″*), 35.8 (CH_2, C9″), 36.3 (CH_2, C9″*), 73.9 (CH, C2″‡), 75.7 (CH, C2″$^{\phi}$), 77.1 (CH, C7″‡), 78.8 (CH, C7″$^{\phi}$), 114.3 (quat., C5″$^{\phi}$), 114.7 (quat., C5″‡), 123.6 (CH, Ph, *m*), 129.6 (CH, Ph, *p*), 129.9 (CH, Ph, *o*), 133.5 (quat., Ph), 154.2 (quat., C5); *m*/*z* (CI, NH_3) 361 (MH^+, 100%), 343 (14), 215 (6), 141 (11), 111 (10), 100 (9), 83 (12); HRMS (CI): Found MH^+, 361.1696; $C_{18}H_{25}N_4O_2S$ requires 361.1698.

(2″*S*,5″*R*,7″*S*) and (2″*S*,5″*S*,7″*S*)-5-(3′-(2″-Methyl-1″,6″-dioxaspiro[4.4]non-7″-yl)-propylsulfonyl)-1-phenyl-1*H*-tetrazole (6) and (7)

To a solution of sulfides **26** and **27** (1 : 1 mixture) (0.15 g, 0.42 mmol) in dichloromethane (2 mL) was added sodium bicarbonate (0.18 g, 2.08 mmol), followed by a solution of *m*-chloroperoxybenzoic acid (0.18 g, 1.04 mmol) in dichloromethane (2 mL) dropwise *via* syringe. The mixture was stirred under an atmosphere of nitrogen at room temperature for 24 h then a solution of saturated aqueous sodium bicarbonate (2.5 mL) and sodium thiosulfate (2.5 mL) added dropwise. The layers were separated and the aqueous layer extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over potassium carbonate and the solvent removed under reduced pressure. The crude oil was purified by flash column chromatography using hexane–diethyl ether (9 : 1) as eluent to yield the *title compounds* **6** and **7** (0.12 g, 71%) as a clear colourless oil and as a 1 : 1 mixture of diastereomers; ν_{max} (film)/cm^{-1}) 2926, 2872, 1635, 1595, 1497, 1461, 1337, 1151, 916, 867, 762, 731, 688; δ_H (300 MHz, $CDCl_3$)‡ 1.19 (1.5H, d, *J* 6.2 Hz, Me‡), 1.24 (1.5H, d, *J* 6.2 Hz, Me$^{\phi}$), 1.23–1.26 (1H, m, H8″A), 1.39–1.52 (2H, m, H3″A, H8″B), 1.63–1.77 (3H, m, H3′, H4″A), 1.84–1.91 (1H, m, H9″A), 1.93–2.15 (5H, m, H2′, H3″B, H4″B, H9″B), 3.73–3.82 (2H, m, H1′), 3.94–3.98 (0.5H, m, H7″$^{\phi}$), 4.01–4.07 (0.5H, m, H7″‡), 4.10–4.21 (1H, m, H2″), 7.56–7.60 (3H, m, Ph, *m* and *p*), 7.62–7.68 (2H, m, Ph, *o*); δ_C (75.5 MHz, $CDCl_3$)‡ 19.0 (CH_2, C2′), 19.2 (CH_2, C2′*), 21.0 (CH_3, Me‡), 22.5 (CH_3, Me$^{\phi}$), 30.2 (CH_2, C8″), 30.5 (CH_2, C8″*), 32.0 (CH_2, C3″), 32.5 (CH_2, C3″*), 33.6 (CH_2, C3′), 35.2 (CH_2, C4″), 35.4 (CH_2, C4″*), 35.9 (CH_2, C9″), 36.4 (CH_2, C9″*), 55.9 (CH_2, C1′), 55.9 (CH_2, C1′*), 74.0 (CH, C2″‡), 76.0 (CH, C2″$^{\phi}$), 76.8 (CH, C7″‡), 78.6 (CH, C7″$^{\phi}$), 114.6 (quat., C5″$^{\phi}$), 114.9 (quat., C5″‡), 125.0 (CH, Ph, *m*), 129.6 (CH, Ph, *p*), 131.3 (CH, Ph, *o*), 133.0 (quat., Ph), 153.4 (quat., C5); *m*/*z* (CI, NH_3) 393 (MH^+, 100%), 375 (28), 183 (10), 119 (15), 111 (26), 89 (23), 83 (31); HRMS (CI): Found MH^+, 393.1601; $C_{18}H_{25}N_4O_4S$ requires 393.1597.

(3′*E*,3*S*,2″*S*,5″*S*,7″*S*)-, (3′*E*,3*S*,2″*S*,5″*R*,7″*S*)-, (3′*Z*,3*S*,2″*S*,5″*S*,7″*S*)- and (3′*Z*,3*S*,2″*S*,5″*R*,7″*S*)-5,7-Dimethoxy-3-[6′-(2″-methyl-1″,6″dioxaspiro[4.4]non-7″-yl)hex-3′-en-1′-yl]-3*H*-isobenzofuran-1-one (28) and (29)

To a solution of sulfones **6** and **7** (30 mg, 0.08 mmol, 1 : 1) in tetrahydrofuran (1 mL), under an atmosphere of nitrogen at −78 °C, was added potassium hexamethyldisilazide (0.20 mL, 0.5 M in toluene, 0.10 mmol) dropwise. The mixture was stirred for 20 min at −78 °C then a solution of aldehyde **5a** (19 mg, 0.08 mmol) in tetrahydrofuran (1 mL) added. The mixture was stirred for 1.5 h at −78 °C then 1 h at rt. Diethyl ether (10 mL) was added followed by saturated aqueous sodium chloride (10 mL). The layers were separated and the aqueous layer washed with diethyl ether (2 × 10 mL). The combined organic layers were dried over potassium carbonate and the solvent removed under reduced pressure. The crude oil was purified by flash column chromatography using hexane–diethyl ether (1 : 1) as eluent to

afford the *title compounds* **28** and **29** (28 mg, 84%) as a colourless oil and as a 1 : 1 mixture of diastereomers; ν_{max} (film)/cm^{-1} 2971, 2248, 2091, 1743, 1614, 1458, 1337, 1217, 1158, 1028, 910, 837, 730; δ_H (300 MHz, $CDCl_3$)‡ 1.19 (1.5H, d, *J* 6.2 Hz, ((*E*)-Me‡ and (*Z*)-Me‡), 1.30 (1.5H, d, *J* 6.2 Hz, ((*E*)-Me$^{\phi}$ and (*Z*)-Me$^{\phi}$), 1.40–1.52 (2H, m, H6′), 1.69–1.81 (3H, m, H3″, H8″A), 1.83–1.91 (1H, m, H8″B), 1.95–2.17 (6H, m, H1′, H4″, H9″), 2.27–2.48 (4H, m, (*E*)-H2′ and (*Z*)-H2′, (*E*)-H5′ and (*Z*)-H5′), 3.89 (3H, s, OMe), 3.89–3.99 (2H, m, H7″), 3.95 (3H, s, OMe), 4.01–4.10 (1H, m, H2″$^{\phi}$), 4.13–4.20 (1H, m, H2″‡), 5.28, 5.35 (each 1H, each dd, *J* 8.5, 3.1 Hz, H3), 5.50–5.62 (2H, m, (*E*)-H3′ and (*Z*)-H3′, (*E*)-H4′ and (*Z*)-H4′), 6.40–6.42 (1H, m, H6), 6.42–6.43 (1H, m, H4); δ_C (75.5 MHz, $CDCl_3$) 21.1 (CH_3, Me‡), 23.1 (CH_3, Me$^{\phi}$), 24.0 (CH_2, (*Z*)-C2′), 24.1 (CH_2, (*Z*)-C5′), 29.7 (CH_3, (*E*)-C2′), 30.2 (CH_2, (*E*)-C5′), 30.2 (CH_2, C8″‡), 30.5 (CH_2, C8″$^{\phi}$), 32.2 (CH_2, C3″‡), 32.6 (CH_2, C3″$^{\phi}$), 34.6, 34.7 (CH_2, C1′), 35.5 (CH_2, C4″‡), 35.6 (CH_2, C9″‡), 36.0 (CH_2, C4″$^{\phi}$), 36.4 (CH_2, C9″$^{\phi}$), 38.9 (CH_2, C6′), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 74.1, 75.9, 76.0 (CH, C2″), 77.2, 78.5, 78.6 (CH, C7″), 79.2 (CH, C3), 97.4 (CH, C6), 98.9 (CH, C4), 106.8 (quat, C7a), 114.4 (quat, C5″$^{\phi}$), 114.9 (quat, C5″‡), 123.4, 123.6 (CH, C3′), 126.1, 126.3 (CH, C4′), 154.7 (quat, C3a), 159.7 (quat, C7), 166.7 (quat, C5), 166.8 (quat, C1); *m*/*z* (EI$^+$) (MH$^+$, 96%), 399 (38), 305 (12), 219 (7), 193 (12), 154 (100), 85 (9); HRMS (EI$^+$): Found M$^+$, 416.2183, $C_{24}H_{32}O_6$ requires 416.2193.

(3*S*,2″*S*,5″*S*,7″*S*)- and (3*S*,2″*S*,5″*R*,7″*S*)-5,7-Dimethoxy-3-[6′-(2″-methyl-1″,6″-dioxaspiro[4.4]non-7″-yl)hex-1′-yl]-3*H*-isobenzofuran-1-one (1a) [*ent*-CJ-12,954] and (2a) [*ent*-CJ-13,014]

To a solution of the above alkenes (2 mg, 0.01 mmol) in tetrahydrofuran : methanol (1 : 1, 2.0 mL) was added potassium carbonate (2 mg, 0.01 mmol) and platinum(IV) oxide (1 mg, catalytic) and the mixture stirred under a hydrogen atmosphere for 4 h. The mixture was filtered through a pad of silica and Celite® and the solvent removed under reduced pressure. The clear oil was purified by flash column chromatography using dichloromethane–acetone (99 : 1–95 : 5) as eluent to afford the *title compounds* **1a** and **2a** (1.7 mg, 85%) as a clear colourless oil and as a 1 : 1 mixture of diastereomers; $[\alpha]_D$ −38.0 (*c* 0.48, $CHCl_3$); ν_{max} (film)/cm^{-1} 2929, 2856, 1755, 1614, 1462, 1337, 1217, 1158, 1104, 1030, 918, 837, 731, 690; δ_H (400 MHz, $CDCl_3$)‡ 1.20 (1.5H, d, *J* 6.2 Hz, Me‡), 1.28 (1.5H, d, *J* 6.2 Hz, Me$^{\phi}$), 1.25–1.35 (4H, m, H3′, H5′), 1.39–1.49 (4H, m, H2′, H4′), 1.61–1.73 (3H, m, H6′, H8″A), 1.83–1.91 (1H, m, H8″B), 1.92–1.97 (2H, m, H3″), 2.00–2.07 (4H, m, H4″, H9″), 2.09–2.14 (2H, m, H1′), 3.89 (3H, s, OMe), 3.90–3.92 (0.5H, m, H7″$^{\phi}$), 3.94 (3H, s, OMe), 3.99–4.04 (0.5H, m, H7″‡), 4.07–4.12 (0.5H, m, H2″$^{\phi}$), 4.16–4.23 (0.5H, m, H2″‡), 5.29 (1H, dd, *J* 8.2, 3.6 Hz, H3), 6.40 (1H, d, *J* 1.7 Hz, H6), 6.41 (1H, d, *J* 1.7 Hz, H4); δ_C (100 MHz, $CDCl_3$) 21.1 (CH_3, Me‡), 23.0 (CH_3, Me$^{\phi}$), 24.6 (CH_2, C2′), 25.7, 25.9 (CH_2, C5′), 29.3, 29.4 (CH_2, C3′), 29.7 (CH_2, C4′), 30.2 (CH_2, C8″‡), 30.7 (CH_2, C8″$^{\phi}$), 32.2 (CH_2, C3″‡), 32.6 (CH_2, C3″$^{\phi}$), 34.8 (CH_2, C1′), 35.6 (CH_2, C6′‡), 35.7 (CH_2, C4″‡), 36.1 (CH_2, C4″$^{\phi}$), 36.5 (CH_2, C9″), 37.3 (CH_2, C6′$^{\phi}$), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 74.0 (CH, C2″‡), 75.8 (CH, C2″$^{\phi}$), 78.1 (CH, C7″‡), 79.9 (CH, C7″$^{\phi}$), 79.9 (CH, C3), 97.3 (CH, C6), 98.6 (CH, C4), 106.9 (quat, C7a), 114.3 (quat, C5″$^{\phi}$), 114.7 (quat, C5″‡), 155.2 (quat, C3a), 159.6 (quat, C7), 166.6 (quat, C5), 168.6 (quat, C1); *m*/*z* (EI$^+$) 418 (M$^+$, 3%), 361 (26), 320 (24), 278 (9), 207 (16), 193 (35), 141 (100), 112 (13), 85 (24), 55 (9); HRMS (EI$^+$): Found MH$^+$, 418.2340, $C_{24}H_{35}O_6$ requires 418.2355.

(3′*E*,3*R*,2″*S*,5″*S*,7″*S*)-, (3′*E*,3*R*,2″*S*,5″*R*,7″*S*)-, (3′*Z*,3*R*,2″*S*,5″*S*,7″*S*)- and (3′*Z*,3*R*,2″*S*,5″*R*,7″*S*)-5,7-Dimethoxy-3-[6′-(2″-methyl-1″,6″-dioxaspiro[4.4]non-7″-yl)hex-3′-en-1′-yl]-3*H*-isobenzofuran-1-one (32) and (33)

To a solution of sulfones **6** and **7** (70 mg, 0.18 mmol, 1 : 1) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen at −78 °C was added potassium hexamethyldisilazide (0.46 mL, 0.5 M in toluene, 0.23 mmol) and stirred for 20 min. A solution of aldehyde **5b** (45 mg, 0.18 mmol) in tetrahydrofuran (2 mL) was added to the mixture and then stirred at −78 °C for 1 h, before being warmed to rt and stirred for 1 h. Saturated aqueous sodium chloride (10 mL) was added to the mixture, followed by diethyl ether (20 mL), and the layers separated. The aqueous layer was extracted with diethyl ether (2 × 20 mL), and the combined organic extracts were dried over potassium carbonate and the solvent removed under reduced pressure. The crude oil was purified by flash column chromatography using dichloromethane–methanol (99 : 1), then hexane–diethyl ether (1 : 1) as eluent to afford the *title compounds* **32** and **33** (57 mg, 76%) as a clear colourless oil and as a 1 : 1 mixture of diastereomers; ν_{max} (film)/cm^{-1} 2966, 2932, 2248, 1755, 1613, 1494, 1461, 1338, 1217, 1158, 1056, 1030, 969, 918, 838, 731; δ_H (300 MHz, $CDCl_3$)‡ 1.18 (1.5H, d, *J* 6.2 Hz, ((*E*)-Me‡ and (*Z*)-Me‡), 1.26 (1.5H, d, *J* 6.2 Hz, ((*E*)-Me$^{\phi}$ and (*Z*)-Me$^{\phi}$), 1.41–1.49 (2H, m, H6′), 1.51–1.65 (1H, m, H8″A), 1.67 (3H, m, H8″B, H3″), 1.94–2.11 (8H, m, H1′, H4″, H5′, H9″), 2.13–2.24 (2H, m, (*E*)-H2′ and (*Z*)-H2′), 3.87 (3H, s, OMe), 3.87–3.89 (1H, m, H7″$^{\phi}$), 3.92 (3H, s, OMe), 3.92–3.98 (1H, m, H7″‡), 4.00–4.08 (1H, m, H2″$^{\phi}$), 4.09–4.21 (1H, m, H2″‡), 5.27 (1H, dd, *J* 8.5, 3.3 Hz, H3), 5.35–5.53 (2H, m, (*E*)-H3′ and (*Z*)-H3′, (*E*)-H4′ and (*Z*)-H4′), 6.39 (2H, s, H4, H6); δ_C (75.5 MHz, $CDCl_3$) 21.1 (CH_3, Me‡), 22.6 (CH_2, (*Z*)-C2′), 23.0 (CH_3, Me$^{\phi}$), 23.6 (CH_2, (*Z*)-C5′), 27.8 (CH_3, (*E*)-C2′), 28.8 (CH_2, (*E*)-C5′), 30.1, 30.3, 30.6, 30.7 (CH_2, C8″), 32.2 (CH_2, C3″‡), 32.6 (CH_2, C3″$^{\phi}$), 34.8 (CH_2, C1′), 35.4 (CH_2, C6′‡), 35.5 (CH_2, C4″‡), 35.6 (CH_2, C9″‡), 36.0 (CH_2, C4″$^{\phi}$), 36.4 (CH_2, C9″$^{\phi}$), 37.1 (CH_2, C6′$^{\phi}$), 55.9 (CH_3, OMe), 55.9 (CH_3, OMe), 74.0 (CH, C2″‡), 75.8 (CH, C2″$^{\phi}$), 77.5 (CH, C7″‡), 79.1 (CH, C7″$^{\phi}$), 79.2 (CH, C3), 97.4 (CH, C6), 98.7 (CH, C4), 106.9 (quat, C7a), 114.3 (quat, C5″$^{\phi}$), 114.7 (quat, C5″‡), 128.2, 128.4 (CH, C3′), 131.5, 131.7 (CH, C4′), 155.1 (quat, C3a), 159.6 (quat, C7), 166.6 (quat, C5), 168.4 (quat, C1); *m*/*z* (FAB$^+$) (MH$^+$, 96%), 399 (38), 305 (12), 219 (7), 193 (12), 154 (100), 85 (9); HRMS (FAB$^+$): Found MH$^+$, 417.2268, $C_{24}H_{33}O_6$ requires 417.2277.

(3*R*,2″*S*,5″*R*,7″*S*)- and (3*R*,2″*S*,5″*S*,7″*S*)-5,7-Dimethoxy-3-[6′-(2″-methyl-1″,6″-dioxaspiro[4.4]non-7″-yl)hex-1′-yl]-3*H*-isobenzofuran-1-one (1b) and (2b)

To a solution of the above alkenes (20 mg, 0.48 mmol) in tetrahydrofuran : methanol (1 : 1, 4 mL) was added potassium carbonate (25 mg, 0.18 mmol) and platinum(IV) oxide (2 mg) and the mixture stirred under an atmosphere of hydrogen for 4 h. The mixture was filtered through a pad of silica and Celite® and the solvent removed under reduced pressure to afford the

title compounds **1b** and **2b** (18 mg, 90%) as a colourless oil and as a 1 : 1 mixture of diastereomers; $[\alpha]_D$ +36.4 (*c* 0.50, $CHCl_3$); ν_{max} (film)/cm^{-1} 2931, 2857, 1755, 1613, 1494, 1462, 1337, 1217, 1159, 1054, 1030, 918, 837, 731, 690; δ_H (300 MHz, $CDCl_3$)‡ 1.19 (1.5H, d, *J* 6.2 Hz, $Me^{\ddagger}$), 1.26 (1.5H, d, *J* 6.2 Hz, Me^{ϕ}), 1.23–1.36 (4H, m, H3′, H5′), 1.38–1.49 (6H, m, H2′, H4′, H6′), 1.62–1.72 (2H, m, H1′A, H8″A), 1.88–1.90 (1H, m, H8″B), 1.92–1.97 (2H, m, H3″), 1.99–2.05 (3H, m, H4″A, H9″), 2.09–2.14 (2H, m, H1′B, H4″B), 3.87 (3H, s, OMe), 3.88–3.90 (0.5H, m, $H7''^{\phi}$), 3.92 (3H, s, OMe), 3.96–4.03 (0.5H, m, $H7''^{\ddagger}$), 4.05–4.08 (0.5H, m, $H2''^{\phi}$), 4.11–4.21 (0.5H, m, $H2''^{\ddagger}$), 5.26 (1H, dd, *J* 7.5, 3.8 Hz, H3), 6.38 (1H, s, H6), 6.41 (1H, s, H4); δ_C (75.5 MHz, $CDCl_3$) 21.1 (CH_3, $Me^{\ddagger}$), 22.9 (CH_3, Me^{ϕ}), 24.5, 24.6 (CH_2, C2′), 25.6, 25.9 (CH_2, C5′), 29.2, 29.4 (CH_2, C3′), 29.6 (CH_2, C4′), 30.2 (CH_2, $C8''^{\ddagger}$), 30.7 (CH_2, $C8''^{\phi}$), 32.2 (CH_2, $C3''^{\ddagger}$), 32.6 (CH_2, $C3''^{\phi}$), 34.8 (CH_2, C1′), 35.6 (CH_2, C6′‡), 35.7 (CH_2, $C4''^{\ddagger}$), 36.1 (CH_2, $C4''^{\phi}$), 36.4 (CH_2, C9″), 37.3 (CH_2, C6′$^{\phi}$), 55.9 (CH_3, OMe), 55.9 (CH_3, OMe), 74.0 (CH, $C2''^{\ddagger}$), 75.7 (CH, $C2''^{\phi}$), 78.0 (CH, $C7''^{\ddagger}$), 79.9 (CH, $C7''^{\phi}$), 79.9 (CH, C3), 97.4 (CH, C6), 98.6 (CH, C4), 106.9 (quat, C7a), 114.2 (quat, $C5''^{\phi}$), 114.7 (quat, $C5''^{\ddagger}$), 155.1 (quat, C3a), 159.6 (quat, C7), 166.6 (quat, C5), 168.4 (quat, C1); *m/z* (FAB^+) 419 (MH^+, 81%), 361 (5), 320 (6), 207 (7), 193 (10), 154 (100), 120 (12), 111 (11) (9); HRMS (FAB^+): Found MH^+, 419.2446, $C_{24}H_{35}O_6$ requires 419.2434.

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References

1 B. J. Marshall and J. R. Warren, *Lancet*, 1984, **323**, 1311.
2 C. Montecucco and M. D. Bernard, *Microbes Infect.*, 2003, **5**, 715.
3 J. Mackay, A. Jemal, N. C. Lee and D. M. Parkin, *The Cancer Atlas*, American Cancer Society, New York, 2nd edn, 2006.
4 C. Stoicov, R. Saffari, X. Cai, C. Hasyagar and J. Houghton, *Gene*, 2004, **341**, 1.
5 E. M. F. Muri and J. S. Williamson, *Mini-Rev. Med. Chem.*, 2004, **4**, 201.
6 J. H. Walsh and W. L. Peterson, *New Engl. J. Med.*, 1995, **333**, 984; B. Rathbone, *Scrip Magazine*, 1993, 25.
7 K. A. Dekker, T. Inagake, T. D. Gootz, K. Kaneda, E. Nomura, T. Sakakibara, S. Sakemi, Y. Sugie, Y. Yamauchi, N. Yoshikawa and N. J. Kojima, *J. Antibiot.*, 1997, **50**, 833.
8 A. Arnone, G. Assante, G. Nasini and O. Vajna dePava, *Phytochemistry*, 1990, **29**, 613; M. A. Gaudliana, L. H. Huang, T. Kaneko and P. C. Watts, *PCT Int. Appl.*, 1996, W0 9605204; CAN 125:58200.
9 M. Mondal and N. P. Argade, *Tetrahedron Lett.*, 2004, **45**, 5693.
10 S. Dallavalle, R. Nannei, L. Merlini, A. Bava and G. Nasini, *Synlett*, 2005, **17**, 2676.
11 M. A. Brimble, C. L. Flowers, J. K. Hutchinson, J. E. Robinson and M. Sidford, *Tetrahedron*, 2005, **61**, 10036.
12 J. E. Robinson and M. A. Brimble, *Chem. Commun.*, 2005, 1560; J. E. Robinson and M. A. Brimble, *Org. Biomol. Chem.*, 2007, DOI: 10.1039/b708265g.
13 A. Bava, M. Clericuzio, G. Giannini, L. Malpezzi, S. V. Meille and G. Nasini, *Eur. J. Org. Chem.*, 2005, **11**, 2292.
14 R. Nannei, S. Dallavalle, L. Merlini, A. Bava and G. Nasini, *J. Org. Chem.*, 2006, **71**, 6277.
15 For a preliminary communication of this work see: M. A. Brimble and C. J. Bryant, *Chem. Commun.*, 2006, 4506.
16 Z. Wang, B. La, J. M. Fortunak, X.-J. Meng and G. W. Kabalka, *Tetrahedron Lett.*, 1998, **39**, 5501.
17 (*a*) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925; (*b*) E. J. Corey, S. Shibata and R. K. Bakshi, *J. Org. Chem.*, 1988, **53**, 2861.
18 A. S. Cotterill, M. Gill, A. Gimenez and N. M. Milanovic, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3269.
19 For a review on the heterocycle-activated modified Julia reaction see: P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2563. For examples of the use of the heterocycle-activated modified Julia reaction using heterocyclic sulfones bearing a spiroacetal functionality see: S. V. Ley, A. C. Humphries, H. Eick, R. Downham, A. R. Ross, R. J. Boyce, J. B. J. Pavey and J. Pietruszka, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3907; T. Shimizu, T. Masuda, K. Hiramoto and T. Nakata, *Org. Lett.*, 2000, **2**, 2153.
20 P. R. Blakemore, W. J. Cole, P. J. Kocienski and A. Morley, *Synlett*, 1998, 26.
21 F. Freeman, D. S. H. L. Kim and E. Rodriguez, *J. Org. Chem.*, 1992, **57**, 1722.
22 Y. Yuasa, J. Ando and S. Shibuya, *J. Chem. Soc., Perkin Trans. 1*, 1996, 793.
23 W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. A. Straub and A. D. Palkowitz, *J. Org. Chem.*, 1990, **55**, 4117.
24 P. E. van Rijn, S. Mommers, R. G. Visser, H. D. Verkruijsse and L. Brandsma, *Synthesis*, 1981, 451.
25 E. M. Carreira and J. Du Bois, *J. Am. Chem. Soc.*, 1994, **116**, 10825.
26 For reviews on the anomeric effect see: P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, New York, 1983; A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, New York, 1983.
27 (*a*) J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Tetrahedron Lett.*, 1991, **32**, 1175; (*b*) P. J. Kocienski, A. Bell and P. R. Blakemore, *Synlett*, 2000, 365; (*c*) J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne and O. Ruel, *Bull. Soc. Chim. Fr.*, 1993, **130**, 856.
28 D. Bondar and L. A. Paquette, *Org. Lett.*, 2005, **7**, 1813.

