Synthesis of the anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ether and the unnatural (2″*S*)-diastereomer†

James E. Robinson and Margaret A. Brimble*

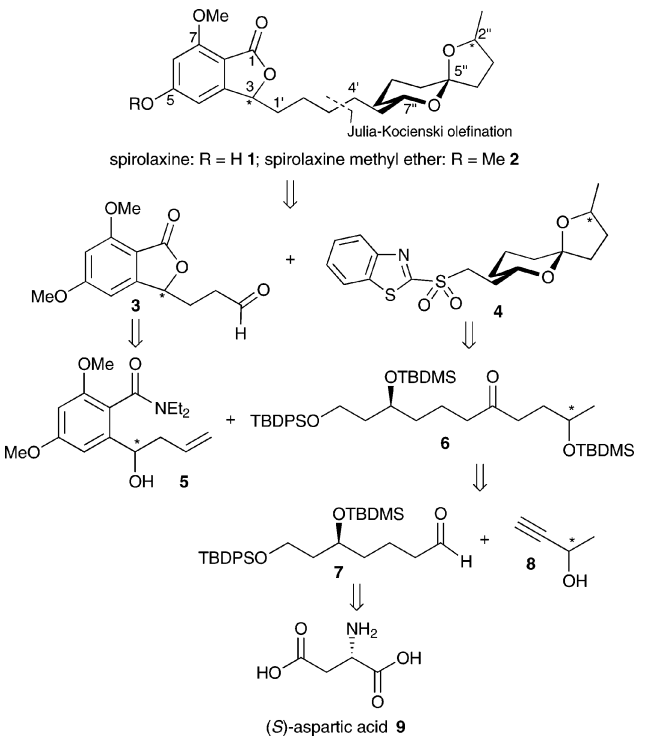
Received 31st May 2007, Accepted 20th June 2007
First published as an Advance Article on the web 11th July 2007
DOI: 10.1039/b708265g

The first enantioselective synthesis of the anti-*Heliocbacter pylori* agent (+)-spirolaxine methyl ether **2b** has been carried out in a convergent fashion establishing that the absolute stereochemistry of the natural product is in fact (3*R*, 2″*R*, 5″*R*, 7″*R*) after initial synthesis of the unnatural (2″*S*)-diastereomer **2a**. The key step in the synthesis of (+)-spirolaxine methyl ether **2b** involved a heterocycle-activated Julia–Kocienski olefination between benzothiazole-based spiroacetal sulfone **4b** and phthalide aldehyde **3a**. (2″*R*, 5″*S*, 7″*S*)-Spiroacetal sulfone **4b** was prepared *via* cyclisation of protected dihydroxyketone **6b**, which in turn was derived from the coupling of the acetylide derived from (*R*)-acetylene **24b** with aldehyde **3a**. Phthalide aldehyde **3a** was prepared *via* intramolecular acylation of bromocarbamate **15**, which was available *via* titanium tetrafluoride-(+)-BINOL-mediated allylation of 3,5-dimethoxybenzaldehyde **13**. Union of the sulfone **4b** and aldehyde **3a** fragments successfully completed the enantioselective synthesis of (+)-spirolaxine methyl ether **2b**. The synthesis of the unnatural (3*R*, 2″*S*, 5″*R*, 7″*R*)-diastereomer of spirolaxine methyl ether **2a** was also undertaken in a similar manner by union of phthalide aldehyde **3a** with (2″*S*, 5″*S*, 7″*S*)-spiroacetal sulfone **4a** derived from (*S*)-acetylene **24a**.

Introduction

Helicobacter pylori has been shown by epidemiologic studies to have an etiological role in several diseases, including gastric and duodenal ulcers, distal gastric cancer and mucosal-associated lymphoid tissue (MALT) lymphoma (cancer of the B cell lymphocytes). It has been estimated that *H. pylori* was the cause of 5.6% of all cancers worldwide in 2002.[1] The microaerophilic, Gram negative bacteria[2] have been estimated to infect the stomach of over half of the world's population,[3] and in most cases infection will persist for the lifetime of an individual without medical intervention.[4] Therapy to eliminate *H. pylori* from the gastroduodenal tract removes the primary cause of gastric and duodenal ulcers, and eliminates the need for an ulcer patient to continue long and costly treatment with H_2 blockers. Current treatment of *H. 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 *H. pylori*.[5]

Spirolaxine **1** and spirolaxine methyl ether **2** (Scheme 1) are produced by various strains of white rot fungi belonging to the genera *Sporotrichum* and *Phanerochaete*.[6] Spirolaxine **1** and spirolaxine methyl ether **2** are potent helicobactericidal compounds and are therefore useful compounds for the treatment of gastroduodenal disorders and the prevention of gastric cancer. Spirolaxine methyl ether **2** contains a 5,7-dimethoxyphthalide nucleus linked through a polymethylene sidechain to a 6,5-spiroacetal group,



Scheme 1

and belongs to the class of endecaketide derivatives that includes phanerosporic and corticiolic acids.[7] Several structurally related phthalide-containing helicobactericidal compounds that contain a 5,5-spiroacetal moiety have also been reported by Dekker *et al.*,[8] which also provide promising leads for the treatment of *H. pylori*-related diseases. Spirolaxine has been reported to exhibit cholesterol lowering activity[9] and more recently studies

Department of Chemistry, University of Auckland, 23 Symonds St, Auckland, New Zealand. E-mail: m.brimble@auckland.ac.nz; Fax: +64 9 3737422

† 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 **3**, **6**, **7**, **12**, **14**–**17** and **18**–**26**. See DOI: 10.1039/b708265g

have shown that it has cytotoxic activity toward endothelial cells (BMEC and Huvec) as well as a variety of tumour cell lines (LoVo and HL60).[10]

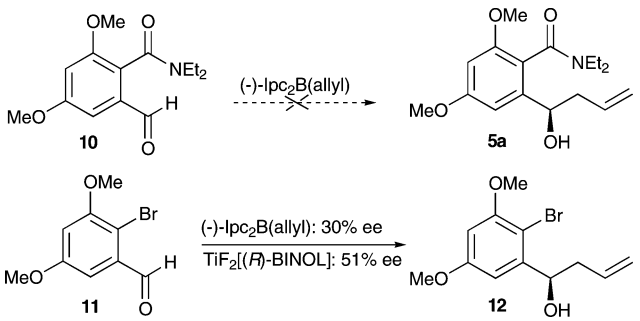
At the outset of this work the absolute and relative stereochemistry of the four stereogenic centres present in spirolaxine **1** and spirolaxine methyl ether **2** had not been established, and a synthesis of these unique helicobactericidal agents had not been reported. We therefore herein report the full details[11] of the first enantioselective total synthesis of (+)-spirolaxine methyl ether **2** that established the absolute configuration of the natural product to be (3*R*, 2″*R*, 5″*R*, 7″*R*). During the course of this work the relative stereochemistry of the four stereocentres of spirolaxine **1** was determined through single-crystal X-ray analysis.[12] A synthesis of (+)-spirolaxine methyl ether **2** was also reported using a Prins cyclisation to form a spiroacetal precursor, and a Wadsworth–Emmons condensation to install the polymethylene chain on the phthalide moiety. However, the absolute stereochemistry of the phthalide moiety was not controlled, thus necessitating separation of two diastereomers formed in the final reduction step.[13]

Results and discussion

In planning our synthesis of spirolaxine methyl ether it was necessary to consider the stereochemistry of the four stereogenic centres, the relative and absolute configuration of which had not been established at the outset of this work. It was anticipated that the [6,5]-spiroacetal ring system would adopt the anomerically-stabilised bis-axial conformation and that the polymethylene side chain at C7″ would occupy the thermodynamically preferred equatorial position. The stereochemistry of the remaining two stereogenic centres however, could not be predicted. Therefore a convergent and flexible synthetic strategy was developed that would allow the stereochemistry at C3 of the phthalide and C2″ of the spiroacetal ring to be varied.

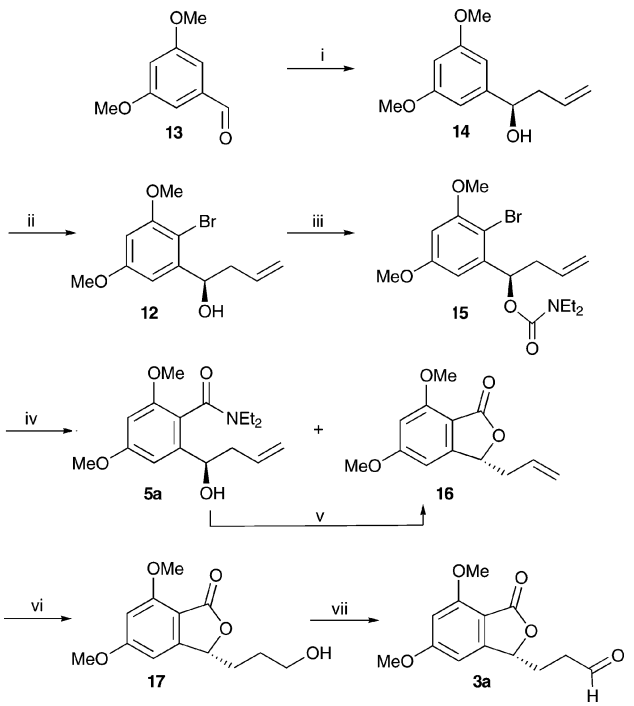
The retrosynthesis adopted (Scheme 1) involves heterocycle-activated Julia–Kocienski olefination of phthalide aldehyde **3** with sulfonyl spiroacetal **4**. Phthalide aldehyde **3** is available *via* lactonisation of alcohol **5**. Both enantiomers of alcohol **5** are available *via* asymmetric allylation, thus providing access to both enantiomers of phthalide aldehyde **3**. Sulfonyl spiroacetal **4** can be prepared *via* acid-catalysed cyclisation of protected dihydroxyketone **6** with the addition of the lithium acetylide of **8** to aldehyde **7** providing the dihydroxyketone precursor **6**. Both enantiomers of acetylene **8** are commercially available, thus facilitating the synthesis of the spiroacetal ring system with either (*R*)- or (*S*)-stereochemistry at C2″. In turn, aldehyde **7**, would be accessible in both enantiomeric forms from the chiral pool reagent (*S*)-aspartic acid **9**.

Initial attention focused on the synthesis of (3*R*, 2″*S*, 5″*R*, 7″*R*)-spirolaxine methyl ether **2a** based on the availability of the chiral starting materials (*S*)-aspartic acid **9** and (*R*)-3-butyn-2-ol **8a**. The synthesis of this diasteromer **2a** as the initial synthetic target then rested on a successful synthesis of (3*R*)-phthalide aldehyde **3a** from (*R*)-homoallylic alcohol **5a** (Scheme 2). Towards this end, the asymmetric allylation of benzaldehyde **10** was investigated following the procedure of Brown *et al.*[14] Disappointingly, allylation using the allylboron reagent derived from (−)-B-allyldiisopinocampheylborane failed to take place. Allylboration of bromobenzaldehyde **11** where the bromide could later be converted to an amide group was next investigated. In this case the allylboration of **11** using (−)-B-allyldiisopinocampheylborane afforded benzylic alcohol **12** with a modest 30% ee. Catalytic asymmetric allylation of benzaldehyde **11** using allyltrimethylsilane in the presence of the catalyst[15] generated from titanium tetrafluoride and (*R*)−(+)-BINOL (10 mol%) afforded the desired (*R*)-benzylic alcohol **12** also with a modest 51% ee.



Scheme 2

At this stage it was postulated that the steric bulkiness of either a diethyl amide or bromide substituent was preventing the formation of the desired benzylic alcohols in high enantiomeric excess. A new synthetic route was therefore proposed wherein introduction of the stereochemistry at the benzylic position took place to allow functionalisation at the *ortho* position. Gratifyingly, titanium tetrafluoride-(*R*)−(+)-BINOL-derived Lewis acid-catalysed addition of allyltrimethylsilane to 3,5-dimethoxybenzaldehdye **13** provided homoallylic alcohol **14** in 76% yield and in 86% ee. (Scheme 3). Regioselective bromination of the aromatic ring using NBS afforded bromide **12** in preparation for subsequent installation of the phthalide functionality at this position.



Scheme 3

Attempts to effect direct carboxylation of bromide **12** proved fruitless. However, Castedo *et al.*[16] have prepared a number of phthalides *via* internal trapping of carbamates derived from benzylic alcohols. With this precedent in mind, alcohol **12** was converted to diethyl carbamate **15** by treatment with sodium hydride and diethyl carbamoyl chloride. Lithium–halogen exchange of **15**, with *tert*-butyllithium (2.2 equiv.) in tetrahydrofuran at −78 °C, provided a mixture of the desired phthalide **16** and diethyl amide **5a**. Direct treatment of this mixture with *p*-toluenesulfonic acid for 12 h provided phthalide **16** in 76% yield over two steps. Hydroboration of **17** then furnished the desired phthalide alcohol **17** that underwent smooth PCC oxidation to the desired (3*R*)-phthalide aldehyde **3a**.

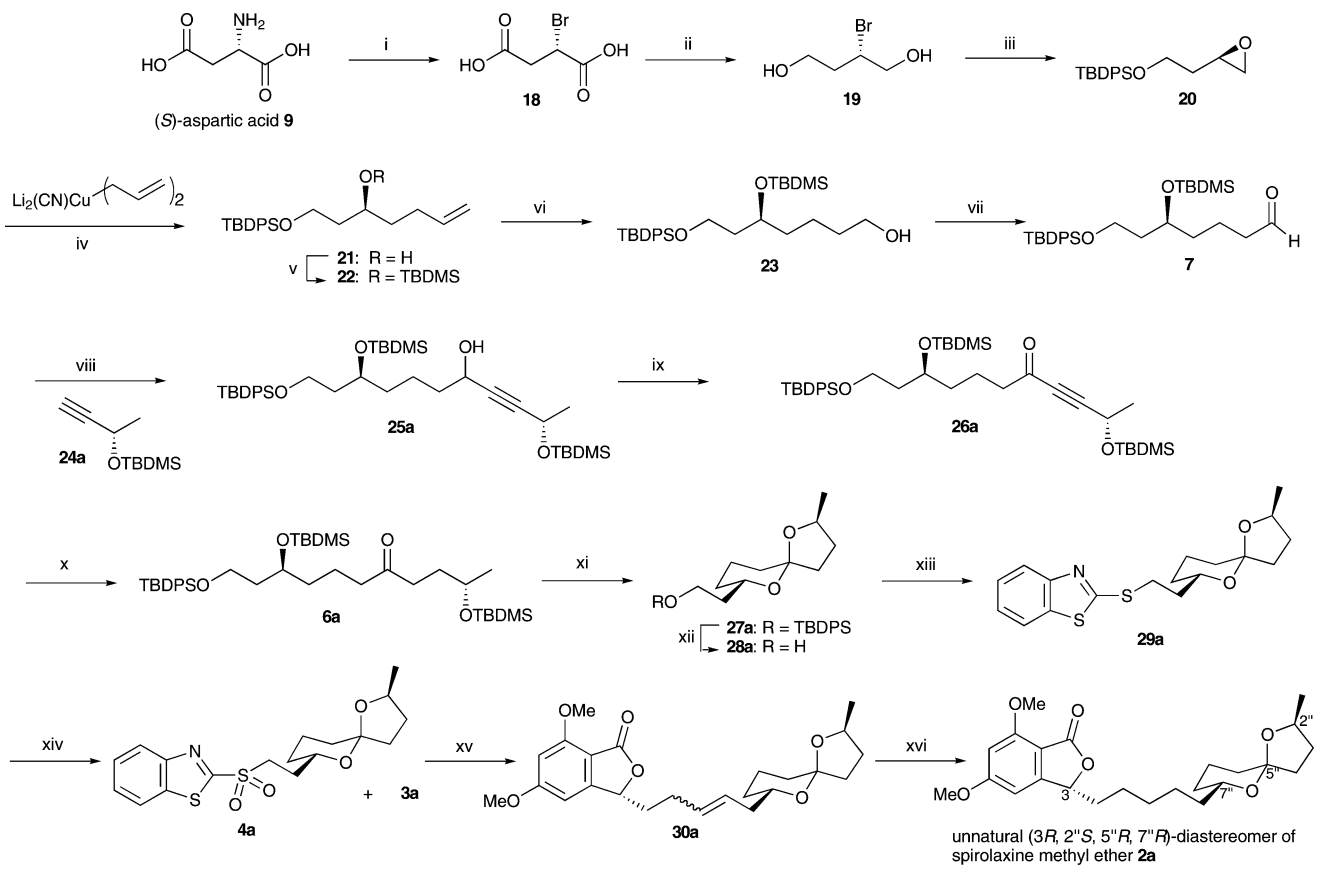
With (3*R*)-phthalide aldehyde **3a** in hand, attention next focused on the synthesis of (2*R*, 7*R*)-spiroacetal sulfone **4a** in preparation for the synthesis of (3*R*, 2″*S*, 5″*R*, 7″*R*)-spirolaxine methyl ether **2a** (Scheme 4) *via* the intermediacy of aldehyde **7**. It was envisaged that aldehyde **7** would be available from (*R*)-epoxide **20**, which could in turn be prepared from (*S*)-aspartic acid **9**. Additionally, the lithium acetylide generated from (*S*)-acetylene **24a**[17] can be used to form C-2 of the spiroacetal ring with the desired stereochemistry.

Bromodiol **19** was initially prepared by treatment of (*S*)-aspartic acid **9** with sodium nitrite in the presence of potassium bromide to afford bromosuccinic acid **18**[18] in 92% yield. Reduction of the two carboxylic acid groups using borane dimethylsulfide complex afforded bromodiol **19** in 93% yield. In an adaptation of the method used by Frick *et al.*[19] (*R*)-epoxide **20**[20,21] was prepared in 82% yield by one-pot intramolecular cyclisation of bromodiol **19** and subsequent protection of the primary alcohol as a silyl ether.

Subsequent allylation of epoxide **20** proved difficult, with initial attempts using allylmagnesium bromide leading to the formation of an inseparable bromohydrin by-product. Treatment of epoxide **20** with allylmagnesium bromide in the presence of copper iodide (15 mol%) or copper bromide dimethyl sulfide complex (15 mol%) at −78 °C also led to the exclusive formation of the bromohydrin. Lipshutz *et al.*[22] have opened epoxides with higher-order diallylcyanocuprates. Diallylcyanocuprate was therefore prepared from lithium chloride, copper(I) cyanide and allyllithium (formed *in situ* by the transmetallation of allyltributyltin and methyllithium), and added *via* cannula to a solution of epoxide **20** in tetrahydrofuran at −78 °C.[23] Gratifyingly, the reaction proceeded to furnish the desired alcohol **21** in 90% yield.

The enantiomeric excess of alcohol **21** was determined to be 94% by examination of the ^{19}F NMR spectrum of the corresponding Mosher ester. After protection as a *tert*-butyldimethylsilyl ether **22** hydroboration of the alkene, using borane dimethylsulfide complex in tetrahydrofuran at 0 °C afforded alcohol **23** in 83% yield. Dess–Martin periodinane oxidation of the primary alcohol to the corresponding aldehyde **7** then proceeded in 86% yield.

With aldehyde **7** in hand, subsequent union with the acetylide derived from (*S*)-acetylene **24a**[17] was investigated. Accordingly, the lithium acetylide was generated from (*S*)-acetylene **24a** using



Scheme 4

n-butyllithium and treated with aldehyde **7** at −78 °C and at −100 °C. Unfortunately, this procedure only afforded a complex mixture of products. The addition of lithium alkynyltrifluoroborates to anhydrides and esters for the synthesis of α,β-acetylenic ketones, has been reported by Brown *et al.*[24] and Yamaguchi *et al.*,[25] hence it was hoped that the use of this less basic nucleophile would favour the desired coupling of **24a** with **7**. Disappointingly, sequential treatment of acetylene **24a** with *n*-butyllithium and boron trifluoride etherate, followed by the addition of aldehyde **7**, also resulted in the formation of a complex mixture of products.

It was postulated that enolate formation was occurring in preference to the desired nucleophilic addition reaction. This postulate was supported by the observations of Brandsma *et al.*,[26] who had encountered a similar problem during the preparation of propargylic alcohols from lithium acetylides and ketones. Brandsma *et al.* successfully circumvented this problem by the inclusion of lithium bromide in the reaction. Lithium bromide has also been employed by Carreira and Du Bois[27] to improve the problematic coupling of an aldehyde and acetylide. Encouraged by these reports, the union of the acetylide of **24a** with aldehyde **7** in the presence of lithium bromide (50 mol%) was undertaken in tetrahydrofuran at −78 °C. Gratifyingly, this procedure furnished acetylenic alcohol **25a** in 86% yield.

Oxidation of acetylenic alcohol **25a** using tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide proceeded smoothly to give the corresponding ynone **26a** in near quantitative yield. Hydrogenation of the alkyne **26a** over 10% Pd/C for 48 h furnished the protected dihydroxyketone **6a** in 86% yield. Selective removal of the *tert*-butyldimethylsilyl ethers with camphorsulfonic acid and concomitant acid-catalysed cyclisation, afforded spiroacetal **27a** in 86% yield. Finally removal of the *tert*-butyldiphenylsilyl ether, with tetrabutylammonium fluoride provided the desired volatile spiroacetal alcohol **28a**.

The structure of spiroacetal alcohol **28a** was assigned on the basis of NMR evidence (Fig. 1). Resonances in the ^{1}H NMR spectrum at δ 4.10 and 4.24, assigned to H7 and H2 respectively, exhibited multiplicities that were indicative of carbocyclic ring formation. In addition, a quaternary carbon resonance in the ^{13}C NMR spectrum at δ 105.9, assigned to C5, was characteristic of a spiroacetal carbon. Due to the thermodynamic stabilisation by the anomeric effect,[28] it was predicted that the acid-catalysed cyclisation of protected dihydroxyketone **6a** would lead to formation of spiroacetal alcohol **28a** where both oxygen atoms of the spiroacetal adopt an axial orientation. This was confirmed by the NOE observed between H7 and the protons of the methyl group at C2.

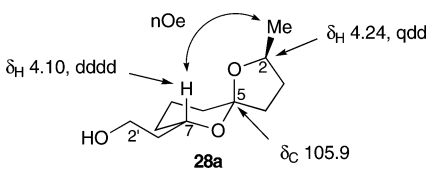


Fig. 1 NMR evidence supporting the structure of spiroacetal alcohol **28**.

In preparation for the Julia–Kocienski olefination of spiroacetal sulfone **4a** with phthalide aldehyde **3a**, alcohol **28a** was treated with 2-mercaptobenzothiazole under Mitsunobu conditions to provide sulfide **29a** in 74% yield. Oxidation to the corresponding sulfone proceeded smoothly in 90% yield using *m*-chloroperoxybenzoic acid in dichloromethane.

Finally it remained to perform the modified Julia–Kocienski olefination of sulfone **4a** and aldehyde **3a**. Accordingly, sulfone **4a** was metallated with lithium diisopropylamide at −78 °C in tetrahydrofuran, and the resultant anion was treated with aldehyde **3a** providing olefin **30a** in a modest 37% yield. Resonances in the ^{1}H NMR‡ spectrum at δ 5.43–5.58, corresponding to H3′, H3′*, H4′ and H4′*, supported the formation of olefin **30a**, as did resonances at δ 127.9, 128.8, 128.9 and 130.0 in the ^{13}C NMR‡ spectrum, corresponding to C3′, C3′*, C4′ and C4′*, respectively. Although the ^{13}C NMR spectrum clearly indicated the presence of both the (*E*)- and (*Z*)-alkenes, the relative ratio of these two diastereomers could not be determined.

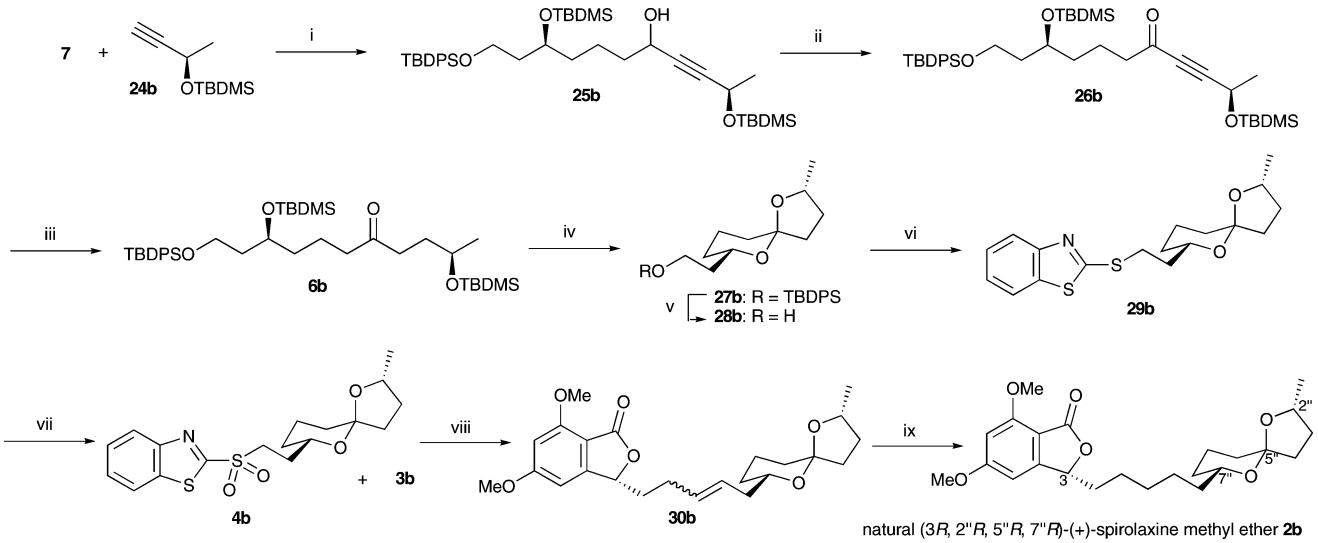
Having finally effected the successful coupling of the spiroacetal and phthalide fragments, it next remained to simply hydrogenate alkenes **30a** to furnish the (3*R*,2″*S*,5″*R*,7″*R*)-diastereomer of spirolaxine methyl ether **2a**. Use of 10% palladium on charcoal as the catalyst afforded a complex mixture of products. Gratifyingly, hydrogenation over Adams' catalyst in tetrahydrofuran proceeded smoothly to provide the (3*R*,2″*S*,5″*R*,7″*R*)-diastereomer of spirolaxine methyl ether **2a**§ in 90% yield.

Comparison of the ^{1}H NMR and ^{13}C NMR data obtained for **2a** with that reported for the natural product,[6,29] however, revealed that the (3*R*, 2″*S*, 5″*R*, 7″*R*)-diastereomer **2a** was in fact an unnatural stereoisomer. Significant differences in the chemical shifts for the (3*R*, 2″*S*, 5″*R*, 7″*R*)-diastereomer of spirolaxine methyl ether **2a** and those reported for the natural product, were observed in the ^{1}H NMR spectrum for the methyl group (δ 1.22 for natural product and 1.27 for **2a**) and H2″ of the spiroacetal ring (δ 4.13 for natural product and 4.22 for **2a**). Similarly, differences were also observed in the ^{13}C NMR spectrum for the methyl group (δ 21.3 for natural product and 23.3 for **2a**) and C2‴ of the spiroacetal ring (δ 73.6 for natural product and 76.6 for **2a**). This, coupled with the fact that the remaining signals were closely matched with those of the natural product, led to the conclusion that the stereochemistry at C2″ was of the wrong configuration. It was therefore proposed that the relative stereochemistry of the natural product was in fact (3*R*, 2″*R*, 5″*R*, 7″*R*).

Having proposed the stereochemistry at C2″ of the natural product to be of (*R*)-configuration and not (*S*), it next remained to synthesise (3*R*, 2″*S*, 5″*R*, 7″*R*)-spirolaxine methyl ether **2b**. It was envisaged that a strategy similar to that developed for the synthesis of (3*R*, 2″*S*, 5″*R*, 7″*R*)-spirolaxine methyl ether **2a** could be used to achieve this goal (Scheme 5). The convergent and flexible nature of the synthetic route adopted herein meant that the only change necessary for the synthesis of (3*R*, 2″*R*, 5″*R*, 7″*R*)-spirolaxine methyl ether **2b**, is the substitution of (*R*)-acetylene **24b** for (*S*)-acetylene **24a**.

Using the conditions developed previously for the synthesis of alcohol **25a**, the lithium acetylide of **24b**, generated with *n*-butyllithium, in the presence of lithium bromide (0.5 equiv.) was

‡ The symbol * is used here to denote the presence of (*E*)- and (*Z*)- isomers.
§ It was expected that spirolaxine methyl ether **2a** would be obtained as a 93 : 7 mixture of diastereomers however, advantageous removal of the minor isomer by flash column chromatography provided **2a** as the sole product.



Scheme 5

treated with aldehyde **7** in tetrahydrofuran at −78 °C (Scheme 5). After stirring for 5 h, alcohol **25b** was furnished in 76% yield. Oxidation of acetylenic alcohol **25b** to corresponding ynone **26b** with tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide proceeded smoothly in 87% yield. Hydrogenation of the alkyne using Adams′ catalyst provided protected dihydroxyketone **6b** in 95% yield after only 6 h, in contrast to the use of palladium on carbon previously for the synthesis of protected dihydroxyketone **6a** in 86% yield, which took 48 h. Selective deprotection of the *tert*-butyldimethylsilyl ethers and concomitant cyclisation of protected dihydroxyketone **6b** to spiroacetal **27b** using camphorsulfonic acid in dichloromethane at 0 °C proceeded in 86% yield. Removal of the *tert*-butyldiphenylsilyl ether using tetrabutylammonium fluoride gave the volatile spiroacetal alcohol **28b** in 83% yield.

Having synthesised spiroacetal alcohol **28b**, preparation of the modified Julia olefination precursor sulfone **4b** was undertaken. Accordingly, alcohol **28b** was treated with 2-mercaptobenzothiazole under Mitsunobu conditions to provide the corresponding sulfide in 62% yield, and the oxidation of which with *m*-chloroperoxybenzoic acid, provided spiroacetal sulfone **4b** in 82% yield. The structure of spiroacetal sulfone **4b** was assigned on the basis of NMR evidence (Fig. 2). Resonances in the ^{1}H NMR spectrum at δ 3.89 and 4.09, assigned to H7″ and H2″ respectively, both exhibited multiplicities that were indicative of carbocyclic ring formation. The chemical non-equivalence of geminal protons at C3, C4, C8, and C9 was also consistent with ring formation. In addition, the ^{13}C NMR spectrum exhibited a quaternary carbon resonance at δ 106.1, which is characteristic of the spiroacetal carbon C5″.

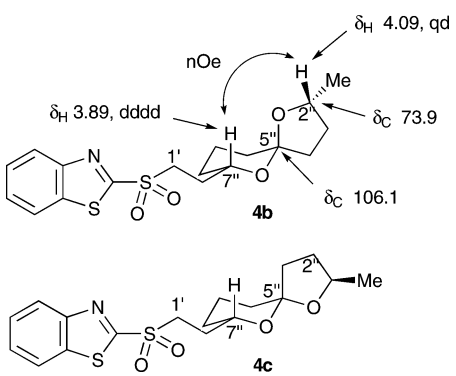


Fig. 2 NMR evidence supporting the structure of spiroacetal sulfone **4**

Similar to spiroacetal sulfone **4a**, the influence of the anomeric effect was also expected to produce a spiroacetal ring system in which the two oxygen atoms would adopt an axial orientation. This prediction was confirmed by the NOE correlation observed between H7″ and H2″, which would be unlikely for the corresponding epimer **4c** in which the oxygen atom of the five-membered ring occupies an equatorial position.

With spiroacetal sulfone **4b** and aldehyde **3a** in hand, it next remained to couple the two fragments in a modified Julia–Kocienski olefination. Accordingly, sulfone **4b** was metallated with lithium diisopropylamide, and the resultant anion treated with aldehyde **3a** in tetrahydrofuran at −78 °C. After 4 h the desired alkene **30b** was isolated in a modest 40% yield.

Resonances in the ^{1}H NMR‡ spectrum at δ 5.41–5.55, corresponding to H3′, H3′*, H4′ and H4′*, supported the formation of alkene **30b**. Signals in the ^{13}C NMR‡ at δ 127.9, 128.8, 129.0 and 129.9, corresponding to C3′, C3′*, C4′ and C4′* respectively, were also consistent with olefination and indicated the presence of both the (*E*)- and (*Z*)- isomers, the relative ratios of which were unable to be determined.

Hydrogenation of olefin **30b** over Adams′ catalyst in tetrahydrofuran afforded (3*R*, 2″*R*, 5″*R*, 7″*R*)-spirolaxine methyl ether **2b**¶ in quantitative yield. The ^{1}H NMR and ^{13}C NMR data for **2b** were identical to that reported for the natural product.[6,29] Gratifyingly, comparison of the optical rotation $\{[\alpha]_D^{20}$ +63.7° (*c* 0.85, $CHCl_3)\}$ with that reported in the literature $\{[\alpha]_D^{30}$ +62° (*c* 0.22 in $CHCl_3)\}$[29]

¶ It was expected that spirolaxine methyl ether **2b** would be obtained as a 93 : 7 mixture of diastereomers however, advantageous partial removal of the minor isomer by flash column chromatography provided a 95 : 5 mixture of diastereomers.

confirmed unequivocally that the absolute stereochemistry of the natural product is in fact (3*R*, 2″*R*, 5″*R*, 7″*R*).

In summary, a convergent enantioselective total synthesis of the anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ether **2b** has been achieved (Scheme 5). The key step of the synthesis involved a modified Julia–Kocienski olefination between spiroacetal sulfone **4b** and phthalide aldehyde **3a**. The synthesis of (+)-(3*R*, 2″*R*, 5″*R*, 7″*R*)-spirolaxine methyl ether **2b** together with the (3*R*, 2″*S*, 5″*R*, 7″*R*)-diastereomer **2a** established the absolute configuration of the four stereogenic centres in the natural product to be (3*R*, 2″*R*, 5″*R*, 7″*R*). The modular nature of the present synthesis based on union of two moieties of predefined stereochemistry also provides an opportunity for the synthesis of other diastereomers of spirolaxine methyl ether, thus providing a potential source of analogues of the natural product for structure–activity studies.

Experimental

(2*S*, 5*R*, 7S)-7-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-methyl-1,6-dioxaspiro[4.5]decane (27a)

To a stirred solution of ketone **6a** (4.48 g, 6.54 mmol) in dichloromethane (65 cm^3) at 0 °C under an atmosphere of nitrogen was added camphorsulfonic acid (3.60 g, 14.38 mmol). After stirring for 2 h, the mixture was filtered through a pad of Celite®, and the solvent removed under reduced pressure. Flash column chromatography using hexane–diethyl ether (8 : 2 to 6 : 4) as eluent afforded the title compound **27a** (2.47 g, 86%) as a yellow oil; $[\alpha]_D$ +117.1 (*c* 0.50 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2934, 2858, 1472, 1428, 1219, 1112, 823, 736 and 702; δ_H (300 MHz, $CDCl_3$): 1.05 (9 H, s, Si^{t}BuPh_2), 1.13–1.19 (1 H, m, H8$_a$), 1.22 (3 H, d, *J* 6.2 Hz, Me), 1.52–1.59 (1 H, m, H8$_b$), 1.59–1.76 (7 H, m, H3$_a$, H4$_a$, H9$_a$, H10 and H1′), 1.76–1.88 (1 H, m, H9$_b$), 1.88–2.00 (2 H, m, H3$_b$ and H4$_b$), 3.75 (2 H, t, *J* 6.8 Hz, H2′), 4.00 (1 H, dddd, *J* 11.5, 7.5, 5.3 and 2.2 Hz, H7), 4.20 (1 H, qdd, *J* 6.2, 6.2 and 1.9 Hz, H2), 7.33–7.44 (6 H, m, Si^{t}BuPh_2, *m* and *p*) and 7.65–7.69 (4 H, m, Si^{t}BuPh_2, *o*); δ_C (75 MHz, $CDCl_3$): 19.2 (quat., Si^{t}BuPh_2), 20.4 (CH_2, C9), 23.4 (CH_3, Me), 26.9 (CH_3, Si^{t}BuPh_2), 31.1 (CH_2, C8), 31.8 (CH_2, C3), 33.5 (CH_2, C10), 39.4 (CH_2, C4 or C1′), 39.5 (CH_2, C1′ or C4), 60.9 (CH_2, C2′), 66.9 (CH, C7), 76.6 (CH, C2), 105.7 (quat., C5), 127.5 (CH, Si^{t}BuPh_2, *m*), 129.5 (CH, Si^{t}BuPh_2, *p*), 134.1 (quat., Si^{t}BuPh_2), 135.6 (CH, Si^{t}BuPh_2, *o*) and 135.6 (CH, Si^{t}BuPh_2, *o**); *m*/*z* (EI): 381 (M−^{t}Bu, 46%), 303 (4), 295 (5), 281 (8), 199 (51), 165 (25), 111 (100), 98 (18), 83 (17) and 55 (19); HRMS (CI, NH_3): Found MH^+, 439.26654. $C_{27}H_{39}O_3Si$ requires *M*, 439.26685.

(2*S*, 5*R*, 7*S*)-7-(2′-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane (28a)

To a stirred solution of silyl ether **27a** (2.46 g, 5.60 mmol) in tetrahydrofuran (30 cm^3) was added tetrabutylammonium fluoride (8.40 cm^3, 8.40 mmol, 1 mol dm^{-3}). After stirring for 2 h, brine (10 cm^3) was added and the mixture extracted with diethyl ether (4 × 40 cm^3). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash column chromatography using hexane–diethyl ether (9 : 1 to 6 : 4) as eluent gave the title compound **28a** (0.76 g, 68%) as a volatile pale yellow oil; $[\alpha]_D$ +60.6 (*c* 1.03 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3435br (OH), 2939, 2871, 1456, 1439, 1377, 1221, 1159, 1115, 1069, 1027, 972, 947, 876 and 862; δ_H (300 MHz, $CDCl_3$): 1.15–1.29 (1 H, m, H8$_a$), 1.25 (3 H, d, *J* 6.3 Hz, Me), 1.43–1.51 (1 H, m, H8$_b$), 1.52–1.68 (7 H, m, H3$_a$, H4$_a$, H9$_a$, H10 and H1′), 1.68–1.85 (1 H, m, H9$_b$), 1.88–2.03 (2 H, m, H3$_b$ and H4$_b$), 3.68–3.72 (2 H, m, H2′), 4.10 (1 H, dddd, *J* 11.4, 8.8, 4.1 and 2.2 Hz, H7) and 4.24 (1 H, qdd, *J* 6.3, 6.3 and 1.8 Hz, H2); δ_C (75 MHz, $CDCl_3$): 20.0 (CH_2, C9), 23.1 (CH_3, Me), 31.0 (CH_2, C8), 31.8 (CH_2, C3), 33.3 (CH_2, C10), 37.9 (CH_2, C1′), 39.3 (CH_2, C4), 61.7 (CH_2, C2′), 71.0 (CH, C7), 76.9 (CH, C2) and 105.9 (quat., C5); *m*/*z* (EI): 185 (M−Me, 3%), 149 (7), 137 (14), 129 (17), 95 (18), 81 (52), 69 (100), 57 (37), 55 (36) and 41 (49); HRMS (CI, NH_3): Found MH^+, 201.14858. $C_{11}H_{21}O_3$ requires *M*, 201.14907.

(2″*S*, 5″*R*, 7″*S*)-2-[2′-(2″-Methyl-1″,6″-dioxaspiro[4.5]dec-7″-yl)-ethylsulfanyl]benzothiazole (29a)

Triphenylphosphine (701 mg, 2.67 mmol) and mercaptobenzothiazole (596 mg, 3.56 mmol) were dissolved in tetrahydrofuran (15 cm^3) and cooled to 0 °C under an atmosphere of nitrogen. To this stirred solution was added alcohol **28a** (357 mg, 1.78 mmol) in tetrahydrofuran (5 cm^3). After stirring for 0.25 h, diethyl azodicarboxylate (0.53 cm^3, 3.21 mmol) was added dropwise *via* syringe. The resultant bright yellow solution was allowed to stir at 0 °C for 2 h. The reaction was quenched by the addition of brine (10 cm^3) and the mixture extracted with diethyl ether (3 × 40 cm^3). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification of the resultant oil by flash column chromatography using hexane–diethyl ether (98 : 2 to 7 : 3) as eluent gave the title compound **29a** (461 mg,. 74%) as a yellow oil; $[\alpha]_D$ +76.3 (*c* 1.00 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2936, 2868, 1459, 1427, 1309, 1237, 1221, 1158, 1113, 1072, 994, 976, 876, 854, 755 and 726; δ_H (400 MHz, $CDCl_3$): 1.18–1.28 (1 H, m, H8″$_a$), 1.30 (3 H, d, *J* 6.2 Hz, Me), 1.56–1.69 (4 H, m, H8″$_b$, H9″$_a$ and H10″), 1.70–1.90 (3 H, m, H3″$_a$, H4″$_a$ and H9″$_b$), 1.91–2.03 (4 H, m, H3″$_b$, H4″$_b$ and H2′), 3.32–3.39 (1 H, m, H1′$_a$), 3.43–3.50 (1 H, m, H1′$_b$), 4.00 (1 H, dddd, *J* 11.3, 9.0, 3.8 and 2.3 Hz, H7″), 4.23 (1 H, qdd, *J* 6.2, 6.2 and 1.9 Hz, H2″), 7.27 (1 H, td, *J* 7.9 and 1.0 Hz, H6), 7.39 (1 H, td, *J* 7.9 and 1.0 Hz, H5), 7.74 (1 H, dd, *J* 7.9 and 1.0 Hz, H7) and 7.85 (1 H, dd, *J* 7.9 and 1.0 Hz, H4); δ_C (100 MHz, $CDCl_3$): 20.2 (CH_2, C9″), 23.4 (CH_3, Me), 30.1 (CH_2, C1′), 30.9 (CH_2, C8″), 32.0 (CH_2, C3″), 33.6 (CH_2, C10″), 36.0 (CH_2, C2′), 39.4 (CH_2, C4″), 68.5 (CH, C7″), 76.9 (CH, C2″), 105.9 (quat., C5″), 120.9 (CH, C7), 121.5 (CH, C4), 124.0 (CH, C6), 125.9 (CH, C5), 135.2 (quat., C7a), 153.4 (quat., C3a) and 167.4 (quat., C2); *m*/*z* (EI): 349 (M^+, 17%), 334 (M−Me, 4), 182 (M−C_7H_5NS, 63), 167 (C_7H_5NS, 100), 125 (29), 111 (68), 98 (69), 83 (14), 55 (25), 43 (26) and 41 (26); HRMS (EI): Found M^+, 349.11669. $C_{18}H_{23}NO_2S_2$ requires *M*, 349.11702.

(2″*S*, 5″*R*, 7″*S*)-2-[2′-(2″-Methyl-1″,6″-dioxaspiro[4.5]dec-7″-yl)-ethylsulfonyl]benzothiazole (4a)

To a solution of thioether **29a** (461 mg, 1.32 mmol) in dichloromethane (5 cm^3) at 0 °C under an atmosphere of nitrogen was added sodium bicarbonate (554 mg, 6.59 mmol) and a solution of *m*-chloroperoxybenzoic acid (569 mg, 3.30 mmol) in

dichloromethane (5 cm^3). After stirring the solution for 12 h, saturated aqueous sodium bicarbonate (2 cm^3) and saturated aqueous sodium thiosulfate (2 cm^3) were added. The aqueous layer was extracted with dichloromethane (3 × 10 cm^3). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The resultant oil was purified by flash column chromatography using hexane–diethyl ether (8 : 2 to 6 : 4) as eluent to afford the title compound **4a** (453 mg, 90%) as a white solid; m.p. 74–77 °C; $[\alpha]_D$ +24.8 (*c* 0.40 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2930, 2870, 1472, 1458, 1328s (SO), 1236, 1221, 1148s (SO), 1072, 1026, 977, 877, 855, 763 and 730; δ_H (400 MHz, $CDCl_3$): 1.12–1.24 (1 H, m, H8″$_a$), 1.24 (3 H, d, *J* 6.2 Hz, Me), 1.50–1.58 (3 H, m, H8″$_b$ and H10″), 1.59–1.72 (3 H, m, H3″$_a$, H4″$_a$ and H9″$_a$), 1.72–1.84 (1 H, m, H9″$_b$), 1.84–2.03 (4 H, m, H3″$_b$, H4″$_b$ and H2′), 3.47 (1 H, ddd, *J* 14.4, 11.3 and 4.8 Hz, H1′$_a$), 3.74 (1 H, ddd, *J* 14.4, 11.3 and 4.8 Hz, H1′$_b$), 3.86–3.92 (1 H, m, H7″), 4.19 (1 H, qdd, *J* 6.2, 6.2 and 1.9 Hz, H2″), 7.57 (1 H, td, *J* 7.3 and 1.5 Hz, H6), 7.64 (1 H, td, *J* 7.3 and 1.5 Hz, H5), 8.01 (1 H, dd, *J* 7.3 and 1.5 Hz, H7) and 8.22 (1 H, dd, *J* 7.3 and 1.5 Hz, H4); δ_C (100 MHz, $CDCl_3$): 20.0 (CH_2, C9″), 23.4 (CH_3, Me), 29.1 (CH_2, C2′), 30.8 (CH_2, C8″), 31.9 (CH_2, C3″), 33.4 (CH_2, C10″), 39.3 (CH_2, C4″), 51.9 (CH_2, C1′), 68.0 (CH, C7″), 76.9 (CH, C2″), 106.0 (quat., C5″), 122.3 (CH, C7), 125.5 (CH, C4), 127.6 (CH, C5), 128.0 (CH, C6), 136.8 (quat., C7a), 152.8 (quat., C3a) and 165.7 (quat., C2); *m*/*z* (EI): 381 (M^+, 2%), 366 (M−Me, 3), 282 (18), 217 (15), 189 (34), 149 (30), 135 (52), 98 (100), 55 (40) and 41 (34); HRMS (EI): Found M^+, 381.10540. $C_{18}H_{23}NO_4S_2$ requires *M*, 381.10685.

(3′*E*, 3*R*, 2″*S*, 5″*R*, 7″*R*)- and (3′*Z*, 3*R*, 2″*S*, 5″*R*, 7″*R*)-5,7-Dimethoxy-3-[5′-(2″-methyl-1″,6″-dioxaspiro[4.5]dec-7″-yl)pent-3′-en-1′-yl]-3*H*-isobenzofuran-1-one (30a)

Sulfone **4a** (181 mg, 0.47 mmol) was dissolved in tetrahydrofuran (9 cm^3) and cooled to −78 °C under an atmosphere of nitrogen. To this stirred solution was added dropwise lithium diisopropylamide (0.52 cm^3, 0.52 mmol, 1 mol dm^{-3}). The resultant deep yellow solution was stirred for 0.75 h before a solution of aldehyde **3a** (119 mg, 0.47 mmol) in tetrahydrofuran (3 cm^3) was added dropwise. After stirring at −78 °C for 4 h, the solution was allowed to slowly warm to room temperature then stirred for 0.5 h. The reaction was quenched by the addition of brine (4 cm^3) and the aqueous layer was extracted with ethyl acetate (3 × 20 cm^3). The combined extracts were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purification of the resultant oil by flash column chromatography using hexane–ethyl acetate (9 : 1 to 1 : 1) as eluent gave the title compound **30a** (73 mg, 37%) as a yellow oil; $[\alpha]_D$ +52.9 (*c* 1.38 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2923, 2850, 1755s (CO), 1605s, 1456, 1337, 1219, 1158, 1059, 1027 and 976; δ_H (300 MHz, $CDCl_3$)‡: 1.09–1.28 (2 H, m, H8″$_a$ and H8″$_a$*), 1.25 (6 H, d, *J* 6.4 Hz, Me and Me*), 1.55–1.66 (8 H, m, H8″$_b$, H8″$_b$*, H9″$_a$, H9″$_a$*, H10″ and H10″*), 1.66–1.83 (8 H, m, H1′$_a$, H1′$_a$*, H3″$_a$, H3″$_a$*, H4″$_a$, H4″$_a$*, H9″$_b$ and H9″$_b$*), 1.89–2.07 (6 H, m, H1′$_b$, H1′$_b$*, H3″$_b$, H3″$_b$*, H4″$_b$ and H4″$_b$*), 2.07–2.18 [4 H, m, (*E*)-H5′ and (*Z*)-H5′], 2.18–2.46 [4 H, m, (*E*)-H2′ and (*Z*)-H2′], 3.78–3.84 (2 H, m, H7″ and H7″*), 3.88 (6 H, s, OMe and OMe*), 3.94 (6 H, s, OMe and OMe*), 4.20 (2 H, qd, *J* 6.4 and 6.4 Hz, H2″ and H2″*), 5.29 (1 H, dd, *J* 7.7 and 3.5 Hz, H3), 5.30 (1 H, dd, *J* 7.7 and 3.5 Hz, H3*), 5.43–5.58 (4 H, m, H3′, H3′*, H4′ and H4′*), 6.38–6.39 (2 H, m, H6 and H6*) and 6.40–6.41 (2 H, m, H4 and H4*); δ_C (75 MHz, $CDCl_3$)‡: 20.3 (CH_2, C9″), 22.8 [CH_2, (*Z*)-C2′], 23.3 (CH_3, Me), 23.4 (CH_3, Me*), 27.9 [CH_2, (*E*)-C2′*], 30.6 (CH_2, C8″), 31.7 (CH_2, C3″), 31.7 (CH_2, C3″*), 33.3 (CH_2, C10″), 33.4 (CH_2, C10″*), 34.1 [CH_2, (*Z*)-C5′], 34.8 (CH_2, C1′), 39.3 (CH_2, C4″), 39.6 [CH_2, (*E*)-C5′], 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 69.7 (CH, C7″), 69.8 (CH, C7″*), 76.6 (CH, C2″), 79.1 (CH, C3), 79.3 (CH, C3*), 97.3 (CH, C6), 98.7 (CH, C4), 105.9 (quat., C5″), 106.8 (quat., C7a), 106.9 (quat., C7a*), 127.9 (CH, C3′), 128.8 (CH, C3′*), 128.9 (CH, C4′), 130.0 (CH, C4′*), 155.1 (quat., C3a), 155.1 (quat., C3a*), 159.6 (quat., C7), 166.6 (quat., C5) and 168.5 (quat., C1); *m*/*z* (EI): 416 (M^+, 2%), 398 (5), 316 (6), 262 (6), 207 (26), 193 (34), 155 (100), 137 (27), 111 (51), 97 (33), 83 (40), 71 (52), 57 (85), 55 (69) and 43 (70); HRMS (EI): Found M^+, 416.22012. $C_{24}H_{32}O_6$ requires *M*, 416.21989.

(3*R*, 2″*S*, 5″*R*, 7″*R*)-5,7-Dimethoxy-3-[5′-(2″-methyl-1″,6″-dioxaspiro[4.5]dec-7″-yl)pent-1′-yl]-3*H*-isobenzofuran-1-one (2a)

Alkene **30a** (12 mg, 0.03 mmol) was dissolved in tetrahydrofuran (10 cm^3) and hydrogenated using a hydrogen-filled double balloon in the presence of platinum(IV) oxide (1.5 mg) for 6 h. The catalyst was removed by filtration through a pad of Celite®, and the solvent removed under reduced pressure. Purification of the resultant oil by flash column chromatography using hexane–ethyl acetate (8 : 2 to 6 : 4) as eluent gave the title compound **2a** (11 mg, 90%) as a yellow oil; $[\alpha]_D$ +51.1 (*c* 1.44 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2934, 2861, 1755s (CO), 1605s, 1494, 1456, 1435, 1337, 1219, 1158, 1051, 1027 and 975; δ_H (300 MHz, $CDCl_3$): 1.14 (1 H, dddd, *J* 13.1, 13.1, 11.5 and 3.9 Hz, H8″$_a$), 1.27 (3 H, d, *J* 6.2 Hz, Me), 1.28–1.48 (8 H, m, H2′, H3′, H4′ and H5′), 1.52–1.80 (7 H, m, H1′$_a$, H3″$_a$, H4″$_a$, H8″$_b$, H9″$_a$ and H10″), 1.81–1.87 (1 H, m, H9″$_b$), 1.94–2.04 (3 H, m, H1′$_b$, H3″$_b$ and H4″$_b$), 3.74–3.82 (1 H, m, H7″), 3.89 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.22 (1 H, qdd, *J* 6.2, 6.2 and 1.6 Hz, H2″), 5.30 (1 H, dd, *J* 7.7 and 3.8 Hz, H3), 6.40 (1 H, apparent s, H6) and 6.42 (1 H, d, *J* 1.6 Hz, H4); δ_C (75 MHz, $CDCl_3$): 20.4 (CH_2, C9″), 23.3 (CH_3, Me), 24.5 (CH_2, C2′), 25.5 (CH_2, C4′), 29.4 (CH_2, C3′), 31.1 (CH_2, C8″), 31.8 (CH_2, C3″), 33.5 (CH_2, C10″), 34.8 (CH_2, C1′), 36.3 (CH_2, C5′), 39.4 (CH_2, C4″), 55.9 (CH_3, OMe), 55.9 (CH_3, OMe), 69.6 (CH, C7″), 76.6 (CH, C2″), 79.9 (CH,C3), 97.3 (CH, C6), 98.6 (CH, C4), 105.8 (quat., C5″), 106.9 (quat., C7a), 155.1 (quat., C3a), 159.5 (quat., C7), 166.6 (quat., C5) and 168.5 (quat., C1); *m*/*z* (EI): 418 (M^+, 8%), 400 (7), 361 (11), 318 (59), 293 (24), 290 (23), 261 (25), 207 (54), 193 (72), 155 (63), 111 (28), 98 (100), 55 (25), 43 (22) and 41 (24); HRMS (EI): Found M^+, 418.23519. $C_{24}H_{34}O_6$ requires *M*, 418.23554.

(2*R*, 5*R*, 9*S*)- and (2*R*, 5*S*, 9*S*)-2,9-Bis-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)undec-3-yn-5-ol (25b)

n-Butyllithium (7.71 cm^3, 12.33 mmol, 1.6 mol dm^{-3}) was added to a stirred solution of (*R*)-silyl ether **24b** (2.08 g, 11.30 mmol) in tetrahydrofuran (30 cm^3) at −78 °C under an atmosphere of nitrogen and the resultant pale yellow solution stirred for 0.5 h before the addition of anhydrous lithium bromide (0.45 g, 5.14 mmol) in tetrahydrofuran (5 cm^3). After 0.25 h, a solution of aldehyde **7** (5.13 g, 10.27 mmol) in tetrahydrofuran (20 cm^3) was

added dropwise and the solution stirred for 5 h. Saturated aqueous ammonium chloride (30 cm^3) was added and the mixture extracted with diethyl ether (3 × 100 cm^3). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash column chromatography using pentane–diethyl ether (95 : 5 to 70 : 30) as eluent afforded the title compound **25b** (5.34 g, 76%) as a yellow oil; $[\alpha]_D$ +19.5 (*c* 4.38 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3400br (OH), 2954, 2930, 2857, 1472, 1463, 1428, 1255, 1152, 1104, 835, 775, 738 and 701; δ_H (300 MHz, $CDCl_3$): 0.02 (3 H, s, Si^{t}Bu*Me*$_2$), 0.05 (3 H, s, Si^{t}Bu*Me*$_2$), 0.16 (3 H, s, Si^{t}Bu*Me*$_2$), 0.17 (3 H, s, Si^{t}Bu*Me*$_2$), 0.90 (9 H, s, Si^{t}BuMe$_2$), 0.95 (9 H, s, Si^{t}BuMe$_2$), 1.10 (9 H, s, Si^{t}BuPh$_2$), 1.44 (3 H, d, *J* 6.5 Hz, H1), 1.46–1.55 (4 H, m, H7 and H8), 1.68–1.77 (4 H, m, H6 and H10), 3.77 (2 H, t, *J* 5.9 Hz, H11), 3.92 (1 H, m, H9), 4.40 (1 H, t, *J* 6.3 Hz, H5), 4.59 (1 H, q, *J* 6.5 Hz, H2), 7.38–7.47 (6 H, m, Si^{t}Bu*Ph*$_2$, *m* and *p*) and 7.69–7.72 (4 H, m, Si^{t}Bu*Ph*$_2$, *o*); δ_C (75 MHz, $CDCl_3$): −4.9 (CH_3, Si^{t}Bu*Me*$_2$), −4.6 (CH_3, Si^{t}Bu*Me*$_2$), −4.5 (CH_3, Si^{t}Bu*Me*$_2$), −4.4 (CH_3, Si^{t}Bu*Me*$_2$), 18.0 (quat., Si^{t}BuMe$_2$), 18.2 (quat., Si^{t}BuMe$_2$), 19.1 (quat., Si^{t}BuPh$_2$), 20.8 (CH_2, C7), 25.4 (CH_3, C1), 25.8 (CH_3, Si^{t}BuMe$_2$), 25.9 (CH_3, Si^{t}BuMe$_2$), 26.9 (CH_3, Si^{t}BuPh$_2$), 36.9 (CH_2, C8), 37.9 (CH_2, C6), 39.8 (CH_2, C10), 58.9 (CH, C2), 60.9 (CH_2, C11), 62.3 (CH, C5), 69.1 (CH, C9), 84.2 (quat., C4), 87.3 (quat., C3), 127.6 (CH, Si^{t}Bu*Ph*$_2$, *m*), 129.5 (CH, Si^{t}Bu*Ph*$_2$, *p*), 133.9 (quat., Si^{t}Bu*Ph*$_2$) and 135.5 (CH, Si^{t}Bu*Ph*$_2$, *o*); *m*/*z* (EI): 625 (M−^{t}Bu$^+$, 2%), 493 (9), 401 (8), 361 (15), 313 (12), 271 (17), 209 (23), 197 (32), 159 (21), 145 (42), 135 (69), 91 (35) and 73 (100); HRMS (FAB): Found MH^+, 683.43464. $C_{39}H_{67}O_4Si_3$ requires *M*, 683.43472.

(2*R*, 9*S*)-2,9-Bis-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)undec-3-yn-5-one (26b)

Alcohol **25b** (4.02 g, 5.88 mmol) was dissolved in dichloromethane (15 cm^3) with 4 Å molecular sieves and cooled to 0 °C under an atmosphere of nitrogen. To this stirred solution was added *N*-methylmorpholine-*N*-oxide (1.03 g, 8.82 mmol) and tetrapropylammonium perruthenate (0.10 g, 0.29 mmol). After stirring at room temperature for 2 h the solvent was removed under reduced pressure. Purification of the resultant residue by flash column chromatography using hexane–diethyl ether (9 : 1 to 7 : 3) as eluent gave the title compound **26b** (3.49 g, 87%) as a yellow oil; $[\alpha]_D$ +18.6 (*c* 1.78 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2955, 2930, 2857, 2213 (C≡C), 1680s (CO), 1472, 1428, 1255, 1156, 1111, 836, 776, 738 and 701; δ_H (300 MHz, $CDCl_3$): 0.02 (3 H, s, Si^{t}Bu*Me*$_2$), 0.05 (3 H, s, Si^{t}Bu*Me*$_2$), 0.13 (3 H, s, Si^{t}Bu*Me*$_2$), 0.16 (3 H, s, Si^{t}Bu*Me*$_2$), 0.87 (9 H, s, Si^{t}BuMe$_2$), 0.92 (9 H, s, Si^{t}BuMe$_2$), 1.06 (9 H, s, Si^{t}BuPh$_2$), 1.39–1.47 (2 H, m, H8), 1.47 (3 H, d, *J* 6.6 Hz, H1), 1.62–1.76 (4 H, m, H7 and H10), 2.53 (2 H, t, *J* 7.4 Hz, H6), 3.73 (2 H, td, *J* 6.4 Hz, J_w 2.1 Hz, H11), 3.90 (1 H, quintet, *J* 5.8 Hz, H9), 4.66 (1 H, q, *J* 6.6 Hz, H2), 7.35–7.45 (6 H, m, Si^{t}Bu*Ph*$_2$, *m* and *p*) and 7.65–7.69 (4 H, m, Si^{t}Bu*Ph*$_2$, *o*); δ_C (75 MHz, $CDCl_3$): −5.0 (CH_3, Si^{t}Bu*Me*$_2$), −4.6 (CH_3, Si^{t}Bu*Me*$_2$), −4.6 (CH_3, Si^{t}Bu*Me*$_2$), −4.4 (CH_3, Si^{t}Bu*Me*$_2$), 18.0 (quat., Si^{t}BuMe$_2$), 18.1 (quat., Si^{t}BuMe$_2$), 19.1 (quat., Si^{t}BuPh$_2$), 19.6 (CH_2, C7), 24.5 (CH_3, C1), 25.7 (CH_3, Si^{t}BuMe$_2$), 25.9 (CH_3, Si^{t}BuMe$_2$), 26.9 (CH_3, Si^{t}BuPh$_2$), 36.4 (CH_2, C8), 39.7 (CH_2, C10), 45.5 (CH_2, C6), 58.8 (CH, C2), 60.8 (CH_2, C11), 68.9 (CH, C9), 82.3 (quat., C4), 93.5 (quat., C3), 127.6 (CH, Si^{t}Bu*Ph*$_2$, *m*), 127.6 (CH, Si^{t}Bu*Ph*$_2$, *m**), 129.5 (CH, Si^{t}Bu*Ph*$_2$, *p*), 129.6 (CH, Si^{t}Bu*Ph*$_2$, *p**), 133.9 (quat., Si^{t}Bu*Ph*$_2$), 135.5 (CH, Si^{t}Bu*Ph*$_2$, *o*) and 187.4 (quat., C5); *m*/*z* (FAB): 623 (M−^{t}Bu$^+$, 1%), 549 (3), 491 (2), 471 (2), 413 (2), 293 (3), 271 (3), 239 (4), 209 (7), 197 (15), 135 (38) and 73 (100); HRMS (FAB): Found MH^+, 681.41812. $C_{39}H_{65}O_4Si_3$ requires *M*, 681.41907.

(2*R*, 9*S*)-2,9-Bis-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)undecan-5-one 6b

Ynone **26b** (3.48 g, 5.11 mmol) was dissolved in a solution of methanol and tetrahydrofuran (10 cm^3, 1 : 1), and hydrogenated using a hydrogen-filled double balloon in the presence of PtO_2 (0.17 g) for 6 h. The catalyst was removed by filtration through a pad of Celite®, and the solvent removed under reduced pressure. Purification of the resultant oil by flash column chromatography using hexane–diethyl ether (9 : 1) as eluent gave the title compound **6b** (3.32 g, 95%) as a yellow oil; $[\alpha]_D$ −1.0 (*c* 3.60 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2955, 2929, 2857, 1716s (CO), 1472, 1428, 1255, 1111, 1005, 836, 774, 738 and 701; δ_H (300 MHz, $CDCl_3$): 0.01 (6 H, s, Si^{t}Bu*Me*$_2$), 0.04 (6 H, s, Si^{t}Bu*Me*$_2$), 0.86 (9 H, s, Si^{t}BuMe$_2$), 0.89 (9 H, s, Si^{t}BuMe$_2$), 1.06 (9 H, s, Si^{t}BuPh$_2$), 1.13 (3 H, d, *J* 6.1 Hz, H1), 1.36–1.45 (2 H, m, H8), 1.53–1.62 (2 H, m, H7), 1.63–1.76 (4 H, m, H3 and H10), 2.34–2.55 (4 H, m, H4 and H6), 3.72 (2 H, td, *J* 6.5 Hz, J_w 1.7 Hz, H11), 3.66–3.92 (2 H, m, H2 and H9), 7.35–7.44 (6 H, m, Si^{t}Bu*Ph*$_2$, *m* and *p*) and 7.65–7.69 (4 H, m, Si^{t}Bu*Ph*$_2$, *o*); δ_C (75 MHz, $CDCl_3$): −4.8 (CH_3, Si^{t}Bu*Me*$_2$), −4.6 (CH_3, Si^{t}Bu*Me*$_2$), −4.4 (CH_3, Si^{t}Bu*Me*$_2$), −3.9 (CH_3, Si^{t}Bu*Me*$_2$), 18.0 (quat., 2 × Si^{t}BuMe$_2$), 19.2 (quat., Si^{t}BuPh$_2$), 19.6 (CH_2, C7), 23.7 (CH_3, C1), 25.9 (CH_3, Si^{t}BuMe$_2$), 26.0 (CH_3, Si^{t}BuMe$_2$), 26.9 (CH_3, Si^{t}BuPh$_2$), 33.2 (CH_2, C3), 36.8 (CH_2, C8), 38.6 (CH_2, C4), 39.7 (CH_2, C10), 42.9 (CH_2, C6), 42.9 (CH_2, C6*), 60.8 (CH_2, C11), 67.6 (CH, C9), 69.0 (CH, C2), 127.6 (CH, Si^{t}Bu*Ph*$_2$, *m*), 129.5 (CH, Si^{t}Bu*Ph*$_2$, *p*), 129.5 (CH, Si^{t}Bu*Ph*$_2$, *p**), 133.9 (quat., Si^{t}Bu*Ph*$_2$), 135.5 (CH, Si^{t}Bu*Ph*$_2$, *o*) and 210.9 (quat., C5); *m*/*z* (FAB): 685 (MH^+, 2%), 627 (M-^{t}Bu, 2), 553 (3), 495 (3), 421 (6), 239 (8), 197 (16), 135 (39) and 73 (100); HRMS (FAB): Found MH^+, 685.44720. $C_{39}H_{69}O_4Si_3$ requires *M*, 685.45037.

(2*R*, 5*S*, 7*S*)-7-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-methyl-1,6-dioxaspiro[4.5]decane (27b)

To a stirred solution of ketone **6b** (3.32 g, 4.85 mmol) in dichloromethane (50 cm^3) at 0 °C under an atmosphere of nitrogen was added camphorsulfonic acid (2.67 g, 10.67 mmol). After stirring for 2 h the solution was filtered through a pad of Celite®, and the solvent removed under reduced pressure. Flash column chromatography using hexane–diethyl ether (8 : 2 to 6 : 4) as eluent afforded the title compound **27b** (1.83 g, 86%) as a yellow oil; $[\alpha]_D$ +22.5 (*c* 1.21 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2933, 2857, 1472, 1428, 1219, 1111, 823, 736 and 701; δ_H (300 MHz, $CDCl_3$): 1.06 (9 H, s, Si^{t}BuPh$_2$), 1.11–1.17 (1 H, m, H8$_a$), 1.20 (3 H, d, *J* 6.6 Hz, Me), 1.28–1.42 (1 H, m, H3$_a$), 1.51–1.59 (1 H, m, H8$_b$), 1.60–1.68 (5 H, m, H9$_a$, H10 and H1′), 1.69–1.78 (1 H, m, H4$_a$), 1.80–1.90 (2 H, m, H4$_b$ and H9$_b$), 2.04 (1 H, dddd, *J* 11.8, 8.8, 6.6 and 6.6 Hz, H3$_b$), 3.67 (1 H, ddd, *J* 10.1, 6.4 and 6.4 Hz, H2′$_a$), 3.85 (1 H, ddd, *J* 10.1, 6.4 and 6.4 Hz, H2′$_b$), 4.00 (1 H, dddd, *J* 11.4, 6.5, 6.5 and 2.1 Hz, H7), 4.13 (1 H, qd, *J* 6.6 and 6.6 Hz, H2), 7.34–7.45

(6 H, m, Si^{t}BuPh_2, *m* and *p*) and 7.65–7.71 (4 H, m, Si^{t}BuPh_2, *o*); δ_C (75 MHz, $CDCl_3$): 19.2 (quat., Si^{t}BuPh_2), 20.4 (CH_2, C9), 21.1 (CH_3, Me), 26.8 (CH_3, Si^{t}BuPh_2), 31.1 (CH_2, C8), 31.3 (CH_2, C3), 33.4 (CH_2, C10), 38.0 (CH_2, C4), 39.3 (CH_2, C1′), 60.5 (CH_2, C2′), 66.9 (CH, C7), 73.4 (CH, C2), 105.9 (quat., C5), 127.5 (CH, Si^{t}BuPh_2, *m*), 129.5 (CH, Si^{t}BuPh_2, *p*), 134.2 (quat., Si^{t}BuPh_2), 134.1 (quat., Si^{t}BuPh_2*), and 135.5 (CH, Si^{t}BuPh_2, *o*); *m*/*z* (EI): 381 (M−^{t}Bu, 54%), 303 (6), 295 (5), 281 (7), 199 (51), 165 (28), 111 (100), 98 (19), 83 (18) and 55 (18); HRMS (CI, NH_3): Found MH^+, 439.26730. $C_{27}H_{39}O_3Si$ requires *M*, 439.26685.

(2*R*, 5*R*, 7*S*)-7-(2′-Hydroxyethyl)-2-methyl-1, 6-dioxaspiro[4.5]decane (28b)

To a stirred solution of silyl ether **27b** (1.81 g, 4.11 mmol) in tetrahydrofuran (15 cm^3) was added tetrabutylammonium fluoride (6.17 cm^3, 6.17 mmol, 1 mol dm^{-3}). After stirring for 2 h, brine (5 cm^3) was added and the mixture extracted with diethyl ether (4 × 20 cm^3). The combined extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. Flash column chromatography using pentane–diethyl ether (9 : 1 to 6 : 4) as eluent gave the title compound **28b** (0.68 g, 83%) as a volatile yellow oil; $[\alpha]_D$ +49.2 (*c* 2.32 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3435br (OH), 2941, 2872, 1456, 1440, 1386, 1364, 1220, 1164, 1065, 1031, 976, 944, 879 and 861; δ_H (300 MHz, $CDCl_3$): 1.25 (3 H, d, *J* 6.6 Hz, Me), 1.28–1.35 (1 H, m, H8$_a$), 1.37–1.48 (1 H, m, H3$_a$), 1.49–1.58 (1 H, m, H8$_b$), 1.61–1.72 (5 H, m, H9$_a$, H10 and H1′), 1.72–1.80 (1 H, m, H4$_a$), 1.82–1.92 (2 H, m, H4$_b$ and H9$_b$), 2.03 (1 H, dddd, *J* 12.1, 8.6, 6.6 and 6.6 Hz, H3$_b$), 3.76 (2 H, m, H2′), 4.03 (1 H, dddd, *J* 12.3, 8.9, 2.8 and 2.8 Hz, H7) and 4.20 (1 H, qd, *J* 6.6 and 6.6 Hz, H2); δ_C (75 MHz, $CDCl_3$): 20.0 (CH_2, C9), 21.2 (CH_3, Me), 30.8 (CH_2, C8), 31.1 (CH_2, C3), 33.2 (CH_2, C10), 37.6 (CH_2, C1′), 38.0 (CH_2, C4), 62.2 (CH_2, C2′), 71.8 (CH, C7), 74.0 (CH, C2) and 106.2 (quat., C5); *m*/*z* (EI): 200 (M^+, 2%), 185 (M−Me, 1), 155 (14), 126 (12), 111 (15), 101 (100), 98 (78), 83 (20), 55 (23), 43 (31) and 41 (28); HRMS (EI): Found M^+, 200.14156. $C_{11}H_{20}O_3$ requires *M*, 200.14124.

(2″*R*,5″*R*,7″*S*)-2-[2′-(2″-Methyl-1″,6″-dioxaspiro[4.5]dec-7″-yl)ethylsulfanyl]benzothiazole (29b)

Triphenylphosphine (1.34 g, 5.12 mmol) and mercaptobenzothiazole (1.14 g, 6.82 mmol) were dissolved in tetrahydrofuran (25 cm^3) and cooled to 0 °C under an atmosphere of nitrogen. To this stirred solution was added alcohol **28b** (0.68 g, 3.41 mmol) in tetrahydrofuran (5 cm^3). After stirring for 0.25 h, diethyl azodicarboxylate (0.53 cm^3, 3.21 mmol) was added dropwise *via* syringe. The resultant bright yellow solution was allowed to stir at 0 °C for 2 h. The reaction was quenched by the addition of brine (10 cm^3) and the mixture extracted with diethyl ether (3 × 40 cm^3). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification of the resultant oil by flash column chromatography using hexane–diethyl ether (98 : 2 to 7 : 3) as eluent gave the title compound **4b** (0.74 g, 62%) as a yellow oil; $[\alpha]_D$ +94.77 (*c* 0.88 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2939, 2870, 1459, 1427, 1309, 1237, 1218, 1162, 1113, 1077, 994, 882, 848, 754 and 726; δ_H (400 MHz, $CDCl_3$): 1.19–1.29 (1 H, m, H8″$_a$), 1.22 (3 H, d, *J* 6.7 Hz, Me), 1.37–1.45 (1 H, m, H3″$_a$), 1.55–1.60 (1 H, m, H8″$_b$), 1.64–1.69 (3 H, m, H9″$_a$ and H10″), 1.76 (1 H, ddd, *J* 12.7, 10.4 and 6.7 Hz, H4″$_a$), 1.82–2.00 (4 H, m, H4″$_b$, H9″$_b$ and H2′), 2.15 (1 H, dddd, *J* 11.9, 8.8, 6.7 and 6.7 Hz, H3″$_b$), 3.35–3.50 (2 H, m, H1′), 3.95 (1 H, dddd, *J* 11.4, 9.0, 3.6 and 2.3 Hz, H7″), 4.18 (1 H, qd, *J* 6.7 and 6.7 Hz, H2″), 7.27 (1 H, td, *J* 7.7 and 1.0 Hz, H6), 7.39 (1 H, td, *J* 7.7 and 1.0 Hz, H5), 7.74 (1 H, d, *J* 7.7 Hz, H7) and 7.85 (1 H, d, *J* 7.7 Hz, H4); δ_C (100 MHz, $CDCl_3$): 20.2 (CH_2, C9″), 21.3 (CH_3, Me), 30.1 (CH_2, C1′), 30.8 (CH_2, C8″), 31.3 (CH_2, C3″), 33.3 (CH_2, C10″), 35.6 (CH_2, C2′), 37.9 (CH_2, C4″), 68.4 (CH, C7″), 73.9 (CH, C2″), 106.1 (quat., C5″), 120.8 (CH, C7), 121.4 (CH, C4), 124.0 (CH, C6), 125.9 (CH, C5), 135.1 (quat., C7a), 153.4 (quat., C3a) and 167.5 (quat., C2); *m*/*z* (EI): 349 (M^+, 19%), 334 (M−Me, 4), 182 (M−C_7H_5NS, 78), 167 (C_7H_5NS, 100), 125 (28), 111 (78), 98 (78), 83 (12), 55 (24), 43 (23), and 41 (26); HRMS (EI): Found M^+, 349.11682. $C_{18}H_{23}NO_2S_2$ requires *M*, 349.11702.

(2″*R*,5″*R*,7″*S*)-2-[2′-(2″-Methyl-1″,6″-dioxaspiro[4.5]dec-7″-yl)ethylsulfonyl]benzothiazole (4b)

To a solution of thioether **29b** (0.74 g, 2.12 mmol) in dichloromethane (10 cm^3) at 0 °C under an atmosphere of nitrogen was added sodium bicarbonate (0.89 g, 10.59 mmol) and a solution of *m*-chloroperoxybenzoic acid (0.91 g, 5.29 mmol) in dichloromethane (10 cm^3). After stirring the solution for 12 h, saturated aqueous sodium bicarbonate (4 cm^3) and saturated aqueous sodium thiosulfate (4 cm^3) were added. The aqueous layer was extracted with dichloromethane (3 × 30 cm^3), and the combined extracts were dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure provided an oil that was purified by flash column chromatography using hexane–diethyl ether (8 : 2 to 6 : 4) as eluent to afford the title compound **4b** (13 g, 82%) as a yellow oil; $[\alpha]_D$ +28.6 (*c* 1.07 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2939, 2871, 1473, 1328s (SO), 1237, 1219, 1147s (SO), 1084, 1062, 993, 980, 941, 853, 763 and 729; δ_H (300 MHz, $CDCl_3$): 1.12–1.25 (1 H, m, H8″$_a$), 1.21 (3 H, d, *J* 6.2 Hz, Me), 1.34–1.45 (1 H, m, H3″$_a$), 1.50–1.58 (1 H, m, H8″$_b$), 1.59–1.67 (3 H, m, H9″$_a$ and H10″), 1.69–1.76 (1 H, m, H4″$_a$), 1.76–1.87 (2 H, m, H4″$_b$ and H9″$_b$), 1.87–2.03 (1 H, m, H2′), 2.03–2.14 (1 H, m, H3″$_b$), 3.49 (1 H, ddd, *J* 14.5, 10.8 and 5.2 Hz, H1′$_a$), 3.73 (1 H, ddd, *J* 14.5, 10.8 and 5.2 Hz, H1′$_b$), 3.89 (1 H, dddd, *J* 11.3, 8.7, 3.2 and 2.6 Hz, H7″), 4.09 (1 H, qd, *J* 6.2 and 6.2 Hz, H2″″), 7.60 (1 H, td, *J* 7.2 and 1.2 Hz, H6), 7.65 (1 H, td, *J* 7.2 and 1.2 Hz, H5), 8.02 (1 H, d, *J* 7.2 Hz, H7) and 8.24 (1 H, d, *J* 7.2 Hz, H4); δ_C (75 MHz, $CDCl_3$): 20.0 (CH_2, C9″), 21.1 (CH_3, Me), 28.8 (CH_2, C2′), 30.6 (CH_2, C8″), 31.2 (CH_2, C3″), 33.2 (CH_2, C10″), 37.7 (CH_2, C4″), 51.8 (CH_2, C1′), 68.1 (CH, C7″), 73.9 (CH, C2″), 106.1 (quat., C5″), 122.3 (CH, C7), 125.4 (CH, C4), 127.6 (CH, C5), 127.9 (CH, C6), 136.8 (quat., C7a), 152.7 (quat., C3a) and 165.6 (quat., C2); *m*/*z* (EI): 381 (M^+, 3%), 366 (M−Me, 3), 282 (15), 205 (18), 189 (33), 149 (26), 135 (39), 98 (100), 55 (32), 43 (27) and 41 (30); HRMS (EI): Found M^+, 381.10666. $C_{18}H_{23}NO_4S_2$ requires *M*, 381.10685.

(3′*E*, 3*R*, 2″*R*, 5″*R*, 7″*R*)- and (3′*Z*, 3*R*, 2″*R*, 5″*R*, 7″*R*)-5,7-Dimethoxy-3-[5′-(2″-methyl-1″,6″-dioxaspiro[4.5]dec-7″-yl)pent-3′-en-1′-yl]-3*H*-isobenzofuran-1-one (30b)

Sulfone **4b** (150 mg, 0.39 mmol) was dissolved in tetrahydrofuran (7.5 cm^3) and cooled to −78 °C under an atmosphere of nitrogen. To this stirred solution was added dropwise lithium

diisopropylamide (0.43 cm^3, 0.43 mmol, 1 mol dm^{-3}). The resultant deep yellow solution was stirred for 0.75 h before a solution of aldehyde **3a** (98 mg, 0.39 mmol) in tetrahydrofuran (2.5 cm^3) was added dropwise. After stirring at −78 °C for 4 h, the solution was allowed to slowly warm to room temperature then stirred for 0.75 h. The reaction was quenched by the addition of brine (3 cm^3) and the aqueous layer was extracted with ethyl acetate (3 × 15 cm^3). The combined extracts were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. The resultant oil was purified by flash column chromatography using hexane–ethyl acetate (9 : 1 to 1 : 1) as eluent to give the title compound **30b** (65 mg, 40%) as a yellow oil; $[\alpha]_D$ +58.6 (*c* 0.97 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2929, 1758s (CO), 1613s, 1462, 1338, 1218, 1159, 1056 and 980; δ_H (400 MHz, $CDCl_3$)‡: 1.08–1.30 (2 H, m, H8″$_a$ and H8″$_a$*), 1.21 (3 H, d, *J* 6.3 Hz, Me), 1.22 (3 H, d, *J* 6.3 Hz, Me*), 1.34–1.42 (2 H, m, H3″$_a$ and H3″$_a$*), 1.55–1.59 (2 H, m, H8″$_b$ and H8″$_b$*), 1.62–1.67 (6 H, m, H9″$_a$, H9″$_a$*, H10″ and H10″*), 1.70–1.79 (4 H, m, H4″$_a$, H4″$_a$*, H1′$_a$ and H1′$_a$*), 1.80–1.89 (4 H, m, H4″$_b$, H4″$_b$*, H9″$_b$ and H9″$_b$*), 1.96–2.03 (2 H, m, H1′$_b$ and H1′$_b$*), 2.03–2.11 [3 H, m, (*E*)-H5′$_a$, H3″$_b$ and H3″$_b$*], 2.12–2.17 [3 H, m, (*E*)-H5′$_b$ and (*Z*)-H5′], 2.18–2.25 [3 H, m, (*E*)-H2′ and (*Z*)-H2′$_a$], 2.26–2.34 [1 H, m, (*Z*)-H2′$_b$], 3.71–3.80 (2 H, m, H7″ and H7″*), 3.89 (3 H, s, OMe), 3.89 (3 H, s, OMe*), 3.95 (6 H, s, OMe and OMe*), 4.13 (1 H, qd, *J* 6.3 and 6.3 Hz, H2″), 4.15 (1 H, qd, *J* 6.3 and 6.3 Hz, H2″*), 5.31 (1 H, dd, *J* 8.3 and 3.4 Hz, H3), 5.33 (1 H, dd, *J* 8.3 and 3.4 Hz, H3*), 5.41–5.55 (4 H, m, H3′, H3′*, H4′ and H4′*), 6.40–6.41 (2 H, m, H6 and H6*) and 6.42 (2 H, s, H4 and H4*); δ_C (100 MHz, $CDCl_3$)‡: 20.3 (CH_2, C9″), 20.3 (CH_2, C9″*), 21.1 (CH_3, Me), 21.2 (CH_3, Me*), 22.8 [CH_2, (*Z*)-C2′], 27.8 [CH_2, (*E*)-C2′], 30.4 (CH_2, C8″), 31.3 (CH_2, C3″), 33.4 (CH_2, C10″), 33.5 (CH_2, C10″*), 34.0 [CH_2, (*Z*)-C5′], 34.8 (CH_2, C1′), 34.8 (CH_2, C1′*), 38.0 (CH_2, C4″), 38.0 (CH_2, C4″*), 39.5 [CH_2, (*E*)-C5′], 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 69.9 (CH, C7″), 73.6 (CH, C2″), 73.7 (CH, C2″*), 79.0 (CH, C3), 79.2 (CH, C3*), 97.3 (CH, C6), 98.7 (CH, C4), 106.1 (quat., C5″), 106.8 (quat., C7a), 106.9 (quat., C7a*), 127.9 (CH, C3′), 128.8 (CH, C3′*), 129.0 (CH, C4′), 129.9 (CH, C4′*), 155.1 (quat., C3a), 155.2 (quat., C3a*), 159.6 (quat., C7), 166.7 (quat., C5) and 168.5 (quat., C1); *m*/*z* (EI): 416 (M^+, 3%), 398 (11), 316 (7), 262 (14), 207 (42), 193 (50), 155 (100), 137 (39), 111 (47), 98 (25), 95 (26), 55 (38) and 41 (36); HRMS (EI): Found M^+, 416.21999. $C_{24}H_{32}O_6$ requires *M*, 416.21989.

(3*R*, 2″*R*, 5″*R*, 7″*R*)-5,7-Dimethoxy-3-[5′-(2″-methyl-1″,6″-dioxaspiro[4.5]dec-7″-yl)pent-1′-yl]-3*H*-isobenzofuran-1-one (2b) (spirolaxine methyl ether)

Alkene **30b** (10 mg, 0.02 mmol) was dissolved in tetrahydrofuran (10 cm^3) and hydrogenated using a hydrogen-filled double balloon in the presence of platinum(IV) oxide (1 mg) for 6 h. The catalyst was removed by filtration through a pad of Celite® and the solvent removed under reduced pressure. Purification of the resultant oil by flash column chromatography using pentane–diethyl ether (4 : 6 to 2 : 8) as eluent gave the title compound **2b** (10 mg, 99%) as a yellow oil; $[\alpha]_D$ +63.7 (*c* 0.85 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2933, 2860, 1756s (CO), 1605s, 1494, 1459, 1432, 1336, 1218, 1158, 1052, 1029 and 980; δ_H (400 MHz, $CDCl_3$): 1.14 (1 H, dddd, *J* 13.0, 13.0, 13.0 and 3.8 Hz, H8″$_a$), 1.23 (3 H, d, *J* 6.6 Hz, Me), 1.25–1.48 (9 H, m, H2′, H3′, H4′, H5′ and H3″$_a$), 1.51–1.56 (1 H, m, H8″$_b$), 1.59–1.72 (4 H, m, H1′$_a$, H9″$_a$ and H10″), 1.74 (1 H, ddd, *J* 12.7, 10.4 and 6.6, H4″$_a$), 1.80–1.89 (2 H, m, H4″$_b$ and H9″$_b$), 1.94–2.01 (1 H, m, H1′$_b$), 2.12 (1 H, dddd, *J* 11.9, 8.8, 6.6 and 6.6 Hz, H3″$_b$), 3.66–3.72 (1 H, m, H7″), 3.89 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.14 (1 H, qd, *J* 6.6 and 6.6 Hz, H2″), 5.30 (1 H, dd, *J* 7.8 and 3.8 Hz, H3), 6.40 (1 H, apparent s, H6) and 6.42 (1 H, d, *J* 1.7 Hz, H4); δ_C (100 MHz, $CDCl_3$): 20.4 (CH_2, C9″), 21.3 (CH_3, Me), 24.5 (CH_2, C2′), 25.4 (CH_2, C4′), 29.3 (CH_2, C3′), 30.9 (CH_2, C8″), 31.3 (CH_2, C3″), 33.5 (CH_2, C10″), 34.8 (CH_2, C1′), 36.1 (CH_2, C5′), 38.0 (CH_2, C4″), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 69.9 (CH, C7″), 73.9 (CH, C2″), 79.9 (CH, C3), 97.3 (CH, C6), 98.6 (CH, C4), 106.0 (quat., C5″), 107.0 (quat., C7a), 155.2 (quat., C3a), 159.6 (quat., C7), 166.6 (quat., C5) and 168.5 (quat., C1); *m*/*z* (EI): 418 (M^+, 6%), 361 (28), 318 (41), 293 (22), 290 (15), 261 (18), 207 (46), 193 (66), 155 (44), 111 (29), 98 (100), 57 (45), 55 (41), 43 (34) and 41 (45); HRMS (EI): Found M^+, 418.23585. $C_{24}H_{34}O_6$ requires *M*, 418.23554. This data was in agreement with that reported in the literature.[6,29]

Acknowledgements

Auckland Uniservices Ltd. is thanked for the award of a postgraduate scholarship to JER.

References

1 J. Mackay, A. Jemal, N. C. Lee and D. M. Parkin, *The Cancer Atlas*, American Cancer Society, New York, 2nd edn, 2006.
2 B. J. Marshall and J. R. Warren, *Lancet*, 1984, **323**, 1311.
3 C. Montecucco and M. D. Bernard, *Microbes Infect.*, 2003, **5**, 715.
4 C. Stoicov, R. Saffari, X. Cai, C. Hasyagar and J. Houghton, *Gene*, 2004, **341**, 1.
5 J. H. Walsh and W. L. Peterson, *N. Engl. J. Med.*, 1995, **333**, 984; B. Rathbone, *Scrip Magazine*, 1993, 25.
6 A. Arnone, G. Assante, G. Nasini and O. Vajna de Pava, *Phytochemistry*, 1990, **29**, 613; M. A. Gaudliana, L. H. Huang, T. Kaneko, P. C. Watts, *PCT Int. Appl.*, 1996, W0 9605204; CAN 125:58200.
7 G. Deffieu, R. Baute, M.-A. Baute and A. Neven, *C. R. Seances Acad. Sci., Ser. D*, 1979, **288**, 647.
8 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.
9 M. J. Blaser, *Clin. Infect. Dis.*, 1992, **15**, 386.
10 S. Penco, C. Pisano and G. Giannini, *WO Pat.* 01/68070.
11 For a preliminary communication of this work see:J. E. Robinson and M. A. Brimble, *Chem. Commun.*, 2005, 1560.
12 A. Bava, M. Clericuszio, G. Giannini, L. Malpezzi, S. V. Meille and G. Nasini, *Eur. J. Org. Chem.*, 2005, **11**, 2292.
13 R. Nannei, S. Dallavalle, L. Merlini, A. Bava and G. Nasini, *J. Org. Chem.*, 2006, **71**, 6277.
14 P. K. Jadhav, K. S. Bhat, P. T. Perumal and H. C. Brown, *J. Org. Chem.*, 1986, **51**, 432.
15 D. R. Gauthier and E. M. Carreira, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2363.
16 M. R. Paleo, C. Lamas, L. Castedo and D. Domínguez, *J. Org. Chem.*, 1992, **57**, 2029.
17 A. S. Cotterill, M. Gill, A. Gimenez and N. M. Milanovic, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3269.
18 T. Shibata, K. Iiono and Y. Sugimura, *Heterocycles*, 1986, **24**, 1331.
19 J. A. Frick, J. B. Klassen, A. Bathe, J. M. Abramson and H. Rapoport, *Synthesis*, 1992, **7**, 621.
20 Y. Mori and M. Suzuki, *Tetrahedron Lett.*, 1989, **38**, 4383.
21 B. Achmatowicz, M. M. Kabat and J. Krajewski, *Tetrahedron*, 1992, **48**, 10201.
22 B. H. Lipshutz, R. Crow, S. H. Dimock, E. L. Ellsworth, R. A. Smith and J. R. Behling, *J. Am. Chem. Soc.*, 1990, **112**, 4063.
23 B. H. Lipshutz and T. R. Elworthy, *J. Org. Chem.*, 1990, **55**, 1695.

24 H. C. Brown, U. S. Racherla and S. M. Singh, *Tetrahedron Lett.*, 1984, **25**, 2411.
25 M. Yamaguchi, K. Shibato, S. Fujiwara and I. Hirao, *Synthesis*, 1986, 421.
26 P. E. van Rijn, S. Mommers, R. G. Visser, H. D. Verkruijsse and L. Brandsma, *Synthesis*, 1981, 459.
27 E. M. Carreira and J. Du Bois, *J. Am. Chem. Soc.*, 1994, **116**, 10825.
28 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.
29 T. Adachi, I. Takagi, K. Kondo, A. Kawashima, A. Kobayashi, I. Taneoka, S. Morimoto, B. M. He and Z. Chen, *PCT Int. Appl.*, 1996, WO 9610020; CAN 125:86482.

