The first enantioselective total synthesis of the anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ether†

James E. Robinson and Margaret A. Brimble*

Received (in Cambridge, UK) 30th November 2004, Accepted 24th December 2004
First published as an Advance Article on the web 26th January 2005
DOI: 10.1039/b418106a

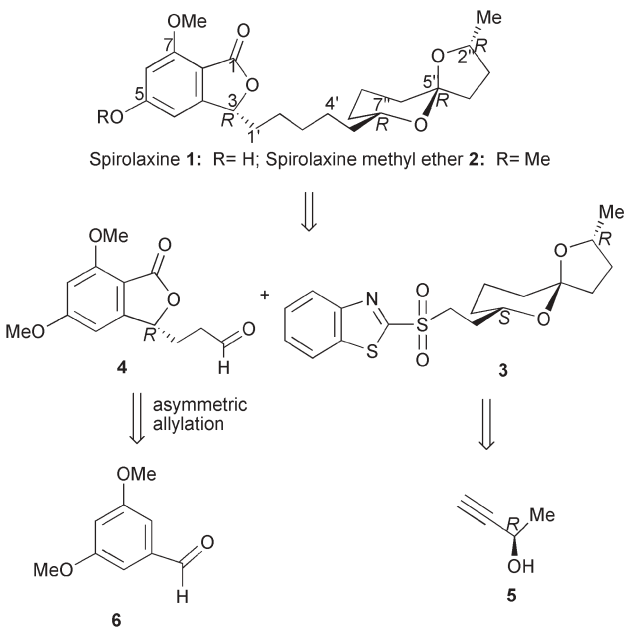
The first enantioselective synthesis of the anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ether has been carried out in a convergent fashion by heterocycle-activated Julia olefination of a spiroacetal-containing sulfone fragment with a phthalide-containing aldehyde fragment. The total synthesis of (+)-spirolaxine methyl ether establishes the absolute stereochemistry of the natural product to be (3*R*,2″*R*,5″*R*,7″*R*).

Gastric and duodenal ulcers affect a significant proportion of the human population worldwide. Initially these ulcers were thought to be caused by the action of digestive fluids (acid and pepsin) on stomach and duodenal tissue and patients were usually treated with H_2 blockers. More recent studies have shown a strong relationship between the presence of the micro-aerophilic Gram-negative bacterium *Helicobacter pylori*, which appears to live beneath the mucus layer of the stomach, and the development of gastric and duodenal ulcers.[1] Therapy to eliminate *Helicobacter 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 *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*.[1]

Spirolaxine **1** and spirolaxine methyl ether **2** are produced by various strains of white rot fungi belonging to the genera *Sporotrichum* and *Phanerochaete*.[2] 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 and belongs to the class of endecaketide derivatives that includes phanerosporic and corticiolic acids.[3] The absolute and relative stereochemistry of the four stereogenic centres present in spirolaxine **1** and spirolaxine methyl ether **2** has not been established and a synthesis of these unique helicobactericidal agents has not been reported to date. We therefore herein report the first enantioselective total synthesis of (+)-spirolaxine methyl ether **2** thus establishing unequivocally that the absolute configuration of the natural product is (3*R*,2″*R*,5″*R*,7″*R*).

In planning our synthesis of spirolaxine methyl ether **2** we decided to prepare the stereoisomer in which the 6,5-spiroacetal ring adopted the anomerically stabilized bis-axial arrangement and the large polymethylene side chain occupied the thermodynamically preferred equatorial position. Having settled on the (5″*R*,7″*R*)-stereochemistry we then decided to develop a flexible approach wherein the stereochemistry at C-3 on the phthalide ring and C-2″ on the spiroacetal ring could be varied. The retrosynthesis adopted (Scheme 1) thus hinged on the union of (3*R*)-phthalide-aldehyde **4** with (2*R*,5*R*,7*S*)-sulfone **3**, wherein the (2*R*)-stereochemistry of sulfone **3** was derived from commercially available (*R*)-3-butyn-2-ol **5** and the use of a titanium-mediated asymmetric allylation of aldehyde **6** using (+)-BINOL introduced the (3*R*)-stereochemistry of phthalide-aldehyde **4** (Scheme 2). Use of (*S*)-3-butyn-2-ol and/or (−)-BINOL allows access to the alternative stereoisomers.

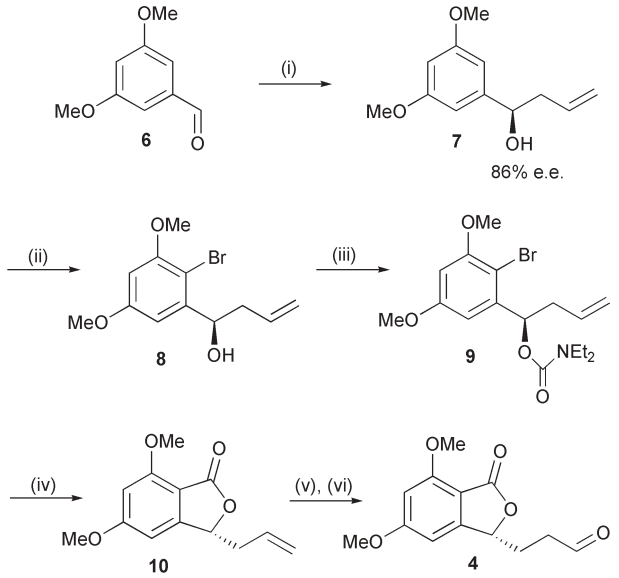
The (3*R*)-stereochemistry in phthalide-aldehyde **4** was set up *via* titanium (+)-BINOL mediated asymmetric allylation[4] of 3,5-dimethoxybenzaldehyde **6** providing (*R*)-homoallylic alcohol **7** in 78% yield and 86% ee (determined by chiral HPLC).‡ Regioselective bromination of the aromatic ring using NBS afforded bromide **8** in preparation for subsequent installation of the phthalide functionality at this position. Attempts to effect direct carboxylation of bromide **8** proved fruitless hence the alcohol was converted to diethylcarbamate **9** with subsequent lithium-halogen exchange followed by intramolecular acylation



Scheme 1

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b418106a/

*m.brimble@auckland.ac.nz



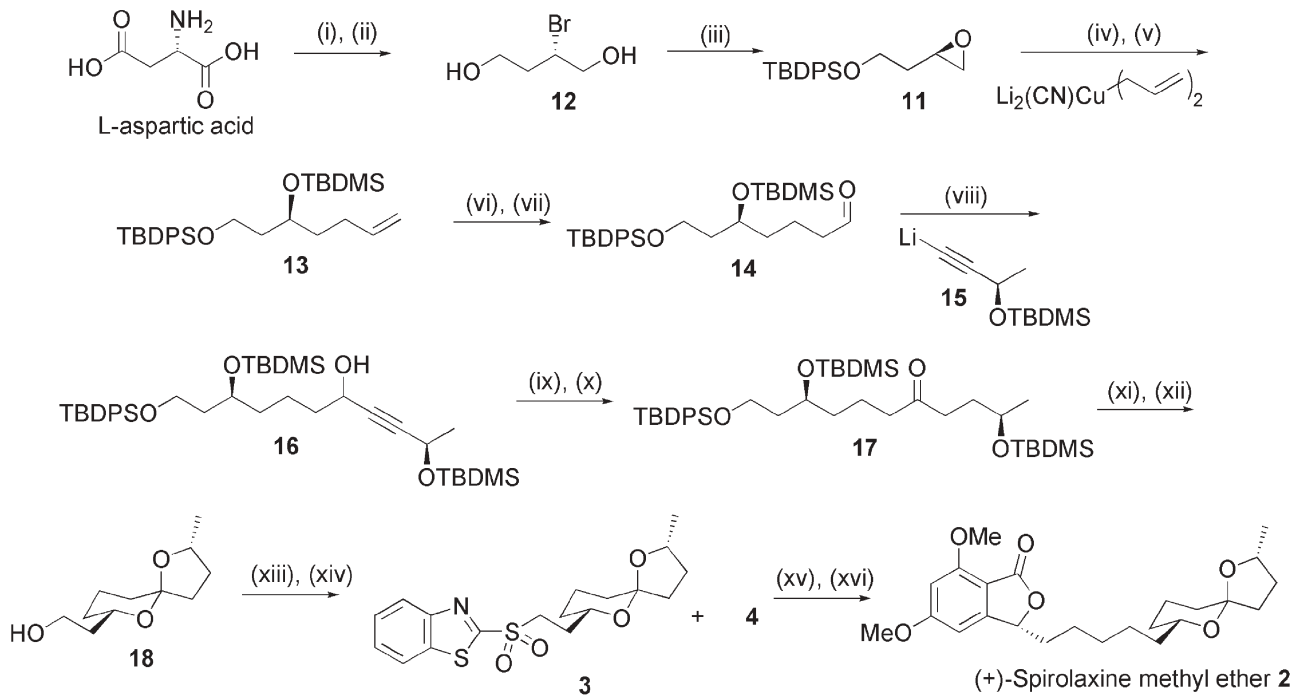
Scheme 2 *Reagents and conditions*: (i) TiF_4, (+)-BINOL, allyltrimethylsilane, CH_2Cl_2–MeCN (97:3), −20 °C, 72 h then *n*-Bu_4NF, 78%; (ii) NBS, $CHCl_3$, reflux, 88%; (iii) NaH, THF, 0 °C then *N,N*-diethylcarbamoyl chloride, 82%; (iv) *t*-BuLi, THF, −78 °C, 45 min then *p*-toluenesulfonic acid, 20 °C, 12 h, 76%; (v) $BH_3.SMe_2$, THF, 0 °C then NaOH, H_2O_2, 56%; (vi) PCC, Celite, 0 °C, 72%.

and lactonisation providing phthalide **10**. Elaboration of the allyl group *via* hydroboration and oxidation then provided the desired phthalide-aldehyde **4**.

For the synthesis of spiroacetal sulfone **3** with the (2*R*,7*S*) configuration it was noted that (*R*)-epoxide **11** was a suitable starting point for introduction of the (*S*)-stereochemistry at C-7. Additionally, lithium (*R*)-acetylide **15**[5] can be used to form C-2 of the spiroacetal ring with the desired (*R*)-stereochemistry (Scheme 3). In an adaptation of the method used by Frick *et al.*,[6] (*R*)-epoxide **11**[7] was prepared by a one-pot intramolecular cyclization of bromo-diol **12** and protection of the primary alcohol as a silyl ether. Bromo-diol **12** in turn was readily available *via* brominative diazotisation of L-aspartic acid followed by reduction of the carboxylic acid groups. Allyl cupration of (*R*)-epoxide **11** afforded a secondary alcohol that was protected as a *tert*-butyldimethylsilyl ether **13**. Subsequent hydroboration and oxidation of the resultant primary alcohol using Dess–Martin periodinane afforded aldehyde **14**.

Addition of aldehyde **14** to lithium acetylide **15** at −78 °C in the presence of lithium bromide[8] provided alcohol **16** in 76% yield. Oxidation of the alcohol to a ketone using tetrapropyl ammonium perruthenate (TPAP) and NMO, followed by reduction of the acetylene, afforded the protected dihydroxyketone **17**. Deprotection of the *tert*-butyldimethylsilyl ethers and facile spirocyclisation was then readily effected using camphorsulfonic acid in dichloromethane to give spiroacetal **18** after cleavage of the *tert*-butyldiphenylsilyl ether with tetrabutylammonium fluoride. The bis-axial stereochemical orientation of spiroacetal **18** is the major thermodynamically-favoured isomer due to its stabilisation by the anomeric affect.[9]

Conversion of the side chain alcohol group in spiroacetal **18** to sulfone **3** proceeded readily in two steps by treatment with



Scheme 3 *Reagents and conditions*: (i) $NaNO_2$, KBr, H_2SO_4, 0 °C, 2 h, 92%; (ii) $BH_3{\cdot}SMe_2$, THF, 0 °C then MeOH, 97%; (iii) NaH (2 equiv.), THF, 0 °C then TBDPSCl, 82%; (iv) cuprate, THF, −78 °C, 2 h, 90%; (v) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 98%; (vi) $BH_3{\cdot}SMe_2$, THF, 0 °C, NaOH, H_2O_2, 83%; (vii) Dess–Martin periodinane, pyridine, CH_2Cl_2, 86%; (viii) LiBr, THF, −78 °C, 76%; (ix) TPAP, NMO, CH_2Cl_2, 78%; (x) H_2, PtO_2, THF, 6 h, 95%; (xi) CSA, CH_2Cl_2, 85%; (xii) TBAF, THF, 0 °C, 83%; (xiii) DEAD, PPh_3, 2-mercaptobenzothiazole; (xiv) *m*-CPBA, CH_2Cl_2, 51% over two steps; (xv) LDA, THF, −78 °C then aldehyde **4**; (xvi) PtO_2, H_2, THF, 2 h, 40% over 2 steps.

mercaptobenzothiazole, PPh_3 and DEAD followed by oxidation using *m*-CPBA. With phthalide-aldehyde **4** and sulfone **3** readily in hand the key heterocycle-activated[10] modified Julia olefination was undertaken.[11] Thus treatment of sulfone **3** with LDA at −78 °C followed by the addition of phthalide-aldehyde **4** provided spirolaxine methyl ether **2** in 40% yield† after careful hydrogenation of the initial olefin over PtO_2. The ^1H and ^{13}C NMR data and optical rotation of the synthetic spirolaxine methyl ether **2** were in agreement with that reported in the literature.[2,12] We also thank Dr Takushi Kaneko (Pfizer R&D, Groton, USA) for an authentic sample of spirolaxine **1** for comparative purposes.

In summary a convergent enantioselective synthesis of the helicobactericidal agent spirolaxine methyl ether **2** has been achieved. The cornerstone of the synthesis entailed a heterocycle-activated modified Julia-Kocienski olefination to join sulfone **3** with phthalide-aldehyde **4**. The successful execution of the synthesis establishes the absolute configuration of the four stereogenic centres in the natural product to be (3*R*,2″*R*,5″*R*,7″*R*).

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

Notes and references

‡ HPLC Conditions: Chiracel® OD-H column, *i*-propanol:hexane 1:9, flow rate 0.5 mL min^{-1}, retention times: 17.8 min (major, *R*-isomer) and 22.4 min (minor, *S*-isomer).

1 M. J. Blaser, *Clin. Infect. Dis.*, 1992, **15**, 386; J. H. Walsh and W. L. Peterson, *New England J. Med.*, 1995, **333**, 984; B. Rathbone, *Scrip Magazine*, 1993, 25.

2 A. Arnone, G. Assante, G. Nasini and O. Vajna de Pava, *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.

3 G. Deffieu, R. Baute, M.-A. Baute and A. Neven, *C. R. Hebd. Seances Acad. Sci., Ser. D*, 1979, **288**, 647.

4 D. R. Gauthier, Jr. and E. M. Carreira, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2363.

5 Spectral data for the (*S*)-enantiomer has been reported see: A. S. Cotterill, M. Gill, A. Gimenez and N. M. Milanovic, *J. Chem. Soc., Perkin Trans 1*, 1994, 3269.

6 J. A. Frick, J. B. Klassen, A. Bathe, J. M. Abramson and H. Rapoport, *Synthesis*, 1992, **7**, 621.

7 The absolute stereochemistry of **11** was confirmed as (*R*) by comparison of its optical rotation with that of the (*S*)-enantiomer as reported by Y. Mori, A. Takeuchi, H. Kageyama and M. Suzuki, *Tetrahedron Lett.*, 1988, **29**, 5423.

8 The effect of LiBr on acetylide addition reactions has been noted: P. E. van Rijn, S. Mommers, R. G. Visser, H. D. Verkruijsse and L. Brandsma, *Synthesis*, **1981**, 451; E. M. Carreira and J. Du Bois, *J. Am. Chem. Soc.*, 1994, **116**, 10825.

9 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.

10 For a review on the heterocycle-activated modified Julia reaction see: P. R. Blakemore, *J. Chem. Soc., Perkin Trans 1*, 2002, 2563.

11 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.

12 T. Adachi, I. Takagi, K. Kondo, A. Kawashima, A. Kobayashi, I. Taneoka, S. Morimoto, B. M. Hi and Z. Chen, *PCT Int. Appl.*, 1996, W0 9610020; CAN 125:86482.

