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Jaspine B (pachastrissamine) and 2-*epi*-jaspine B: synthesis and structural assignment

Elin Abraham, Stephen G. Davies,* Paul M. Roberts, Angela J. Russell and James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK

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Abstract—Jaspine B (pachastrissamine), which was isolated in 2002, is a naturally occurring anhydrophytosphingosine which displays potent biological activity, and as such has attracted much attention from synthetic chemists in recent years, with 14 syntheses reported to date. This review delineates the isolation of jaspine B, and laboratory total syntheses of jaspine B, 2-*epi*-jaspine B and analogues, which serves to confirm their structure and stereochemistry.

Contents

* Corresponding author. E-mail: steve.davies@chem.ox.ac.uk

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1. Introduction

Phytosphingosines **1**–**4** are a sub-class of the sphingoid bases, and consist of a 1,3,4-trihydroxy-2-amino unit at the head of a long hydrocarbon chain. By far the most abundant phytosphingosine is D-*ribo*-phytosphingosine **1**, with 18 carbon atoms in the hydrocarbon chain, although smaller amounts of other chain lengths have been detected. Sphingolipids are essential components of eukaryotic cells[1] and phytosphingolipids exhibit important physiological properties.[2,3] As a result, there has been much interest in their synthesis, and this was the subject of a review in 2002.[4] Jaspine B **5**, also know as pachastrissamine, was the first naturally occurring anhydrophytosphingosine isolated,[5] which also displays potent biological activity (vide infra). Since its isolation in 2002, there has been a great deal of interest from synthetic chemists concerning the total synthesis of jaspine B **5**, its C(2)-epimer (2-*epi*-jaspine B **6**) and their analogues (Fig. 1).

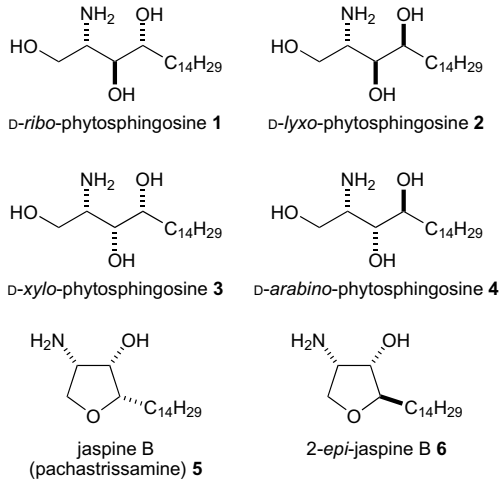
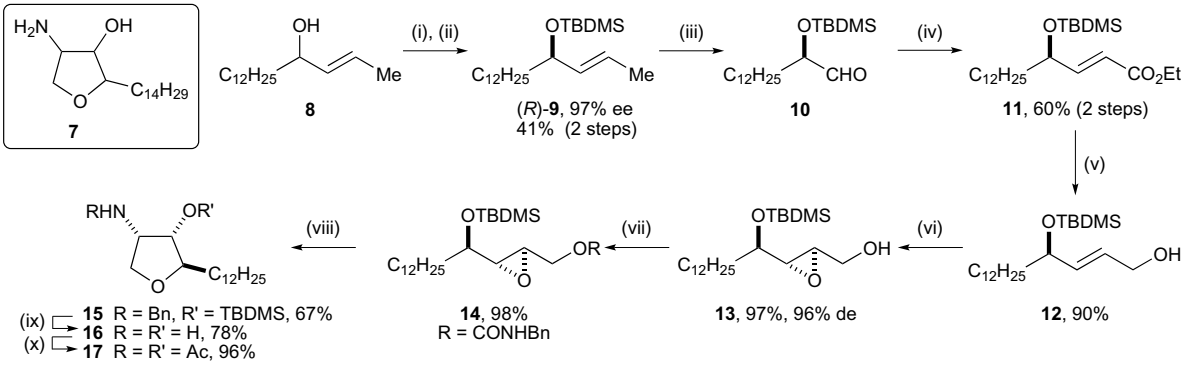


Figure 1. Structures of the C_{18} phytosphingosines **1**–**4** and the anhydrophytosphingosines jaspine B **5** and 2-*epi*-jaspine B **6**.

2. Syntheses of anhydrophytosphingosines prior to the isolation of jaspine B

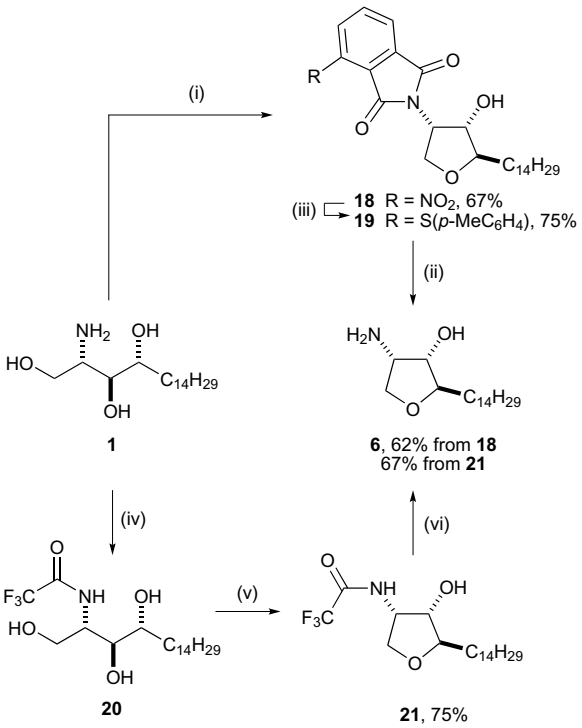
In 1959 the first report of an anhydrophytosphingosine **7** appeared, although a stereochemical assignment was not given.[6] Subsequently, its structure and relative configuration were assigned by analogy with the 'truncated' analogue **16**, bearing a $C_{12}H_{25}$ side chain. In this synthesis allylic alcohol **8**, which was prepared from Grignard addition of dodecylmagnesium bromide to crotonaldehyde, was kinetically resolved under Sharpless asymmetric epoxidation conditions with (+)-diisopropyl tartrate [(+)-DIPT] to afford an enantioenriched sample of (*R*)-**8** in 97% ee,[7] which upon O-silylation afforded (*R*)-**9** in 41% yield over two steps. Ozonolysis of (*R*)-**9** followed by Horner–Wadsworth–Emmons olefination of the resultant aldehyde **10** gave **11** in 60% overall yield over two steps. Reduction of the ester functionality within **11** was achieved with diisobutylaluminium hydride (DIBAL-H) to give allylic alcohol **12** in 90% yield, which was oxidised under Sharpless asymmetric epoxidation conditions with (−)-DIPT to give epoxide **13** in 97% yield and 96% de. Treatment of **13** with benzylisocyanate gave urethane **14** in 98% yield, and subsequent base-mediated epoxide opening gave tetrahydrofuran derivative **15** in 67% yield. The configuration of **15** was determined by conversion to the corresponding *N*,*O*-diacetyl derivative **17** by sequential desilylation, debenzylation and acetylation with Ac_2O to give **17** in 75% yield over two steps; subsequent ^1H NMR NOE studies on **17** supported a (2*R*,3*S*,4*S*)-configuration (Scheme 1).[8]

More recently (2001), the synthesis of an authentic sample of 2-*epi*-jaspine B **6** was reported by Kim et al., starting from D-*ribo*-phytosphingosine **1**.[9] Initial treatment of **1** with 3-nitrophthalic acid at reflux under Dean–Stark conditions is reported to give tetrahydrofuran derivative **18** in 67% isolated yield, with hydrazine-mediated N-deprotection giving **6** in 62% yield. In order to produce a crystalline derivative, tetrahydrofuran **18** was also treated with sodium *p*-tolylthiolate via nucleophilic displacement of the aromatic nitro group to give **19**,[10] the structure of which was established by X-ray crystallography. Kim et al. also



Scheme 1. Reagents and conditions: (i) $Ti(O^iPr)_4$, (+)-DIPT, $^tBuO_2H$, CH_2Cl_2, −20 °C, 15 h; (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 12 h; (iii) O_3, CH_2Cl_2, −78 °C then Me_2S, −78 °C to rt; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, C_6H_6, 60 °C to rt, 15 min; (v) DIBAL-H, hexane, 0 °C to rt, 12 h; (vi) $Ti(O^iPr)_4$, (−)-DIPT, $^tBuO_2H$, CH_2Cl_2, −20 °C, 21 h; (vii) BnNCO, Et_3N, CH_2Cl_2, rt, 12 h; (viii) NaH, THF, rt, 12 h; (ix) HF, H_2O, MeCN, 70 °C, 2 h then Pd/C, cyclohexene, HCl (1 M, aq), MeOH, reflux, 2 h; (x) Ac_2O, pyridine, 70 °C, 1.5 h.

report that treatment of *N*-trifluoroacetyl D-*ribo*-phytosphingosine **20** with *p*-toluenesulfonyl chloride (TsCl) in pyridine effected cyclisation to tetrahydrofuran derivative **21** in 75% yield, which upon deprotection also gave **6** in 67% yield, with identical spectroscopic data (Scheme 2).[9]



Scheme 2. Reagents and conditions: (i) 3-nitrophthalic acid, PhMe, reflux, 3 h; (ii) NH_2NH_2, H_2O, EtOH reflux, 2 h; (iii) NaH, HS(*p*-MeC_6H_4), DMF, 25 °C, 2 h; (iv) F_3CCO_2Et, EtOH, 25 °C, 16 h; (v) TsCl, pyridine, 25 °C, 16 h; (vi) K_2CO_3, MeOH, 25 °C, 16 h.

3. Isolation of jaspine B (pachastrissamine)

In 2002, studies on the marine sponge *Pachastrissa* sp. by Higa and co-workers[5] led to the isolation of an anhydrophytosphingosine derivative which they named pachastrissamine **5** (Fig. 2). Shortly after, in an independent study, Debitus and co-workers reported the isolation of two anhydrophytosphingosines from the marine sponge *Jaspis* sp.,[11] which they named jaspines A **22** and B **5**; pachastrissamine and jaspine B being identical (Fig. 2). Both jaspines A **22** and B **5** display biological activity;[5] jaspine B **5** in particular being the most potent compound isolated from the *Jaspis* genus to date against the A549 human lung carcinoma cell line. At the present time 11 enantiospecific syntheses of jaspine B **5** have been reported, utilising D-*ribo*-phytosphingosine,[12] L-serine,[13] D-galactose,[14] D-xylose,[15] D-glucose,[16] (*R*)-glycidol[17] and D-tartaric acid,[18] as the sources of chirality. Three asymmetric syntheses of jaspine B **5** have also been disclosed: in addition to the procedure reported by us (employing a diastereoselective lithium amide conjugate addition),[19] two other strategies have appeared which both employ the Sharpless asymmetric dihydroxylation reaction.[20] Two syntheses of 'truncated' analogues **23** and **24** (bearing C_5H_{11} and C_8H_{17} side chains) have also emerged, based upon manipulation of L-xylose[21] and Sharpless asymmetric epoxidation,[22] respectively. Several syntheses of the C(2)-epimeric analogues, with C_8H_{17}, $C_{12}H_{25}$ and $C_{14}H_{29}$ side chains, **25**,[22] **16**[8a,b] and **6**,[9,12,19] are also known (Fig. 2).

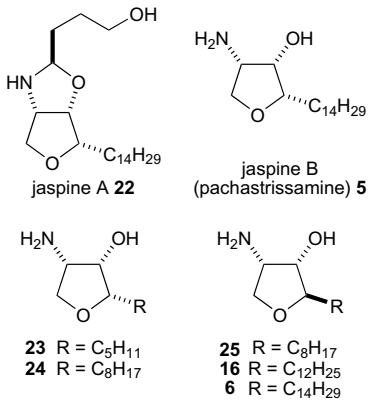


Figure 2. Structures of jaspines A **22** and B (pachastrissamine) **5** and other synthetic analogues **6**, **16** and **23**–**25**.

3.1. Stereochemical assignment

In their original isolation paper, Higa et al. reported extensive NMR analyses suggesting a 2-alkyl-3-hydroxy-4-amino moiety. Importantly, in the key region of the ^1H and ^{13}C NMR spectra corresponding to the tetrahydrofuran ring (δ_H 3.3–4.2 ppm and δ_C 51–86 ppm), the naturally occurring sample of jaspine B **5** did not match the data for the C(2)-epimer **6** (2-*epi*-jaspine B) or the $C_{12}H_{25}$ side-chain analogue **16** that had been reported previously,[8a] and in fact showed marked differences. After the conversion of jaspine B **5** to the corresponding *N*-acetyl and *N*,*O*-diacetyl derivatives **26** and **27**, Higa et al. determined the relative configuration of jaspine B **5** by ^1H NMR NOE analysis of the *N*,*O*-diacetyl derivative **27**, which indicated the all-*cis* relationship of the substituents around the tetrahydrofuran ring. The (2*S*,3*S*,4*S*)-absolute configuration of the natural product was then established using the Mosher method, by conversion of *N*-acetyl jaspine B **26** to the corresponding (*R*)- and (*S*)-2-methoxy-2-trifluoromethylphenylacetyl (MTPA) derivatives.[23] In their independent

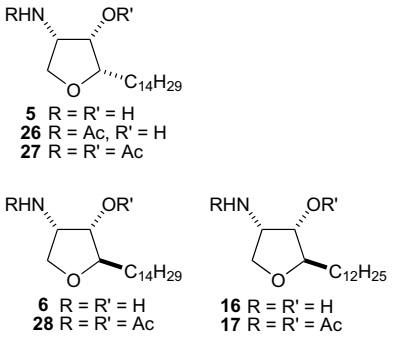


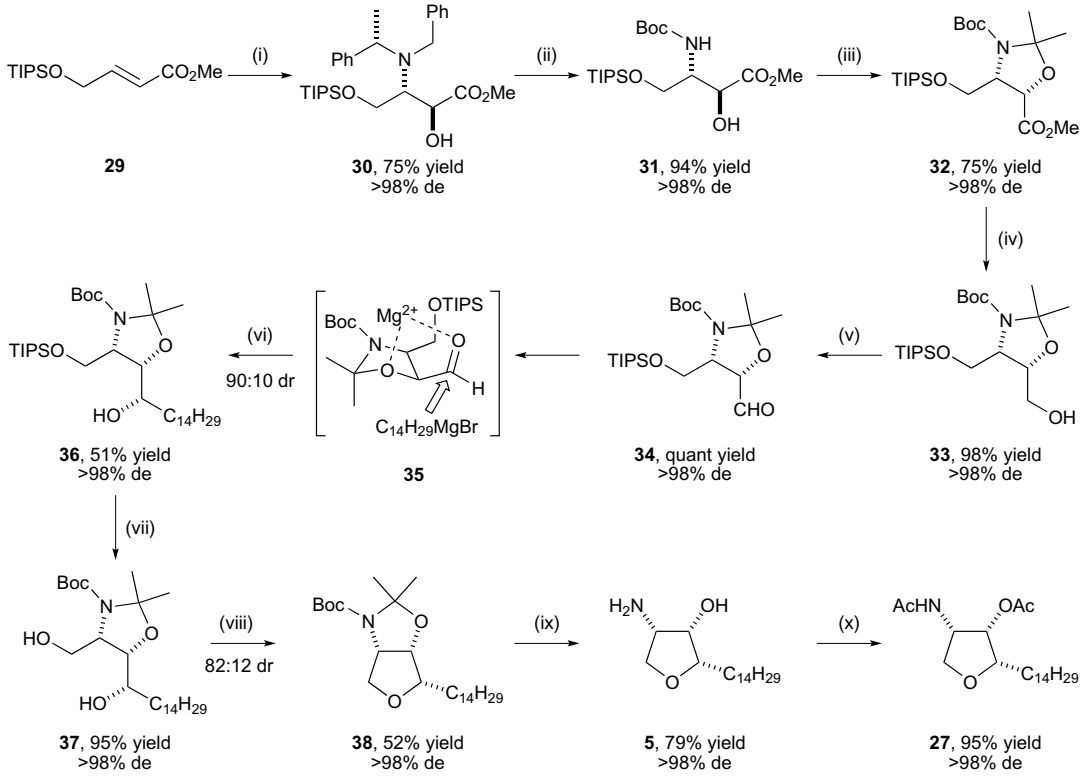
Figure 3. Structures of jaspine B **5**, 2-*epi*-jaspine B **6**, the 'truncated' $C_{12}H_{25}$ side-chain analogue **16** and the corresponding acetate derivatives **17** and **26**–**28**.

study, Debitus et al. also converted jaspine B **5** to the corresponding *N*-acetyl and *N*,*O*-diacetyl derivatives **26** and **27**, and compared the ^{1}H and ^{13}C NMR data with that of the known $C_{12}H_{25}$ side-chain *N*,*O*-diacetyl derivative **17**,[8a,b] which also indicated an all-*cis* relationship of the substituents around the tetrahydrofuran ring. The absolute configuration of the natural product was then determined, also by the Mosher method, as (2*S*,3*S*,4*S*) (Fig. 3).

4. Syntheses of jaspine B (pachastrissamine)

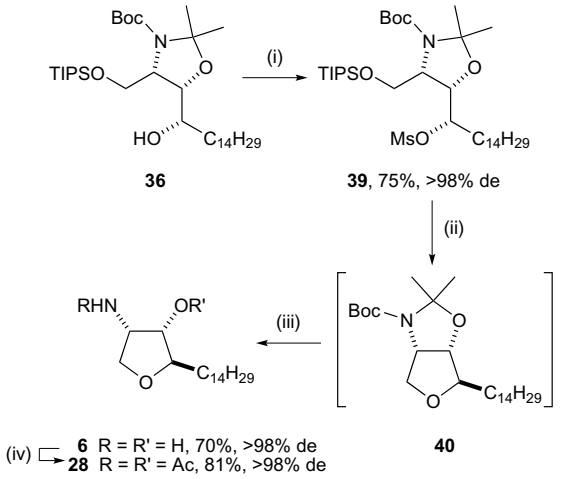
4.1. Synthesis of jaspine B via lithium amide conjugate addition

We have recently reported an asymmetric synthesis of jaspine B **5**, which employs the conjugate addition of a homochiral lithium amide as the key step.[19b,c,24] Thus, α,β-unsaturated ester **29** was treated with lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, with subsequent enolate oxidation with (+)-(camphorsulphonyl)-oxaziridine [(+)-CSO][25] affording α-hydroxy-β-amino ester **30** in 75% yield and >98% de. Protecting group manipulation furnished oxazolidine ester **32** in 71% yield over two steps. Reduction of **32** with DIBAL-H, followed by re-oxidation with 2-iodoxybenzoic acid (IBX), gave aldehyde **34** which was immediately treated with tetradecylmagnesium bromide. This gave a chromatographically separable 90:10 mixture of alcohols, with the major diastereoisomer (4*S*,5*S*,1′*S*)-**36** isolated in 51% yield and >98% de.[26] The preferential addition of tetradecylmagnesium bromide to the *Si* face of aldehyde **34**, giving alcohol (4*S*,5*S*,1′*S*)-**36** as the major diastereoisomeric product, is consistent with the 1,2-addition reaction proceeding via a chelated Cram model **35**.[28] Desilylation of **36** with tetrabutylammonium fluoride (TBAF) gave diol **37** in 95% isolated yield. Optimum conditions for the selective formation of tetrahydrofuran **38** from diol **37** were heating at 80 °C with 3 equiv of tosyl chloride and 4-dimethylaminopyridine (DMAP) for 8 h, which gave quantitative conversion to an 82:18 mixture of diastereoisomeric tetrahydrofurans, with subsequent chromatographic separation giving the major diastereoisomer **38** in 52% yield and >98% de. Subsequent global deprotection of **38** and recrystallisation gave jaspine B **5** in 79% yield (10% overall yield in nine steps from α,β-unsaturated ester **29**) (Scheme 3). Our synthetic sample of jaspine B **5** showed good agreement with the isolation data, although there were significant discrepancies with some reported syntheses of jaspine B **5**. To facilitate a full comparison with all the existing literature data (including 2-*epi*-jaspine B **6** and the *N*,*O*-diacetyl derivatives of both diastereoisomers **27** and **28**), authentic samples of these compounds were synthesised. 2-*epi*-Jaspine B **6** was synthesised from intermediate alcohol **36** via initial mesylation with methanesulfonyl chloride (MsCl) to give **39**, followed by desilylation with TBAF and in situ cyclisation of the



Scheme 3. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 12 h; (iii) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, reflux, 12 h; (iv) DIBAL-H, CH_2Cl_2, 0 °C, 6 h; (v) IBX, DMSO, rt, 12 h; (vi) $C_{14}H_{29}MgBr$, THF, 0 °C to rt, 6 h; (vii) TBAF, THF, rt, 12 h; (viii) TsCl, DMAP, pyridine, reflux, 8 h; (ix) HCl (2 M, aq), MeOH, 50 °C, 6 h, then KOH (2 M, aq); (x) Ac_2O, DMAP, pyridine, rt, 12 h.

resultant primary oxyanion species to give tetrahydrofuran **40**. Tetrahydrofuran **40** proved inseparable by chromatography from the silicon-containing by-products formed in the desilylation reaction and therefore acidic hydrolysis was undertaken giving 2-*epi*-jaspine B **6**, after basification and recrystallisation, in 70% yield (14% overall yield in 10 steps from α,β-unsaturated ester **29**) and >98% de (Scheme 4). The corresponding *N*,*O*-diacetyl derivatives of both jaspine B **5** and 2-*epi*-jaspine B **6** were generated upon the treatment of the free bases with Ac_2O in pyridine



Scheme 4. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, rt, 12 h; (ii) TBAF, THF, rt, 12 h; (iii) HCl (2 M, aq), MeOH, 50 °C, 6 h, then KOH (2 M, aq); (iv) Ac_2O, DMAP, pyridine, rt, 12 h.

to give **27** and **28** in 95% and 81% yields, respectively (Schemes 3 and 4).

Our spectroscopic data for these compounds revealed that there are clear differences between the ^{1}H NMR spectra for jaspine B **5** and 2-*epi*-jaspine B **6**, and also between the ^{1}H NMR spectra for the corresponding *N*,*O*-diacetyl derivatives **27** and **28**. One characteristic difference between the spectra for jaspine B **5** and 2-*epi*-jaspine B **6** is that the natural product **5** has a peak at 3.91 ppm for one of the C(5) protons, whereas 2-*epi*-jaspine B **6** has a corresponding resonance at 4.11–4.15 ppm: there are no peaks in the ^{1}H NMR spectrum of jaspine B **5** above 4 ppm (Fig. 4). The most striking difference between the two diastereoisomeric *N*,*O*-diacetyl derivatives **27** and **28** concerns the peaks corresponding to C(3)*H*: for the *N*,*O*-diacetyl jaspine B **27** this appears at 5.38 ppm, whereas for the corresponding C(2)-epimer **28** the peak is observed at 4.95–4.97 ppm (Fig. 5).

Within our laboratory, ^{1}H NMR NOE analyses of *N*,*O*-diacetyl derivatives **27** and **28** were supportive of the assigned relative configurations of the tetrahydrofuran rings. Furthermore, single crystal X-ray analysis of **27** unambiguously confirmed the all-*cis* relationship of the substituents around the ring,[19a] and determination of a Flack parameter[29] for the structure of −0.04(15), which satisfies the criterion for a reliable assignment of absolute configuration of a material known to be homochiral,[29] confirmed the reported absolute (2*S*,3*S*,4*S*)-configuration of the natural product (originally determined by Higa et al.[5] using the Mosher method)[23] unambiguously (Fig. 6).

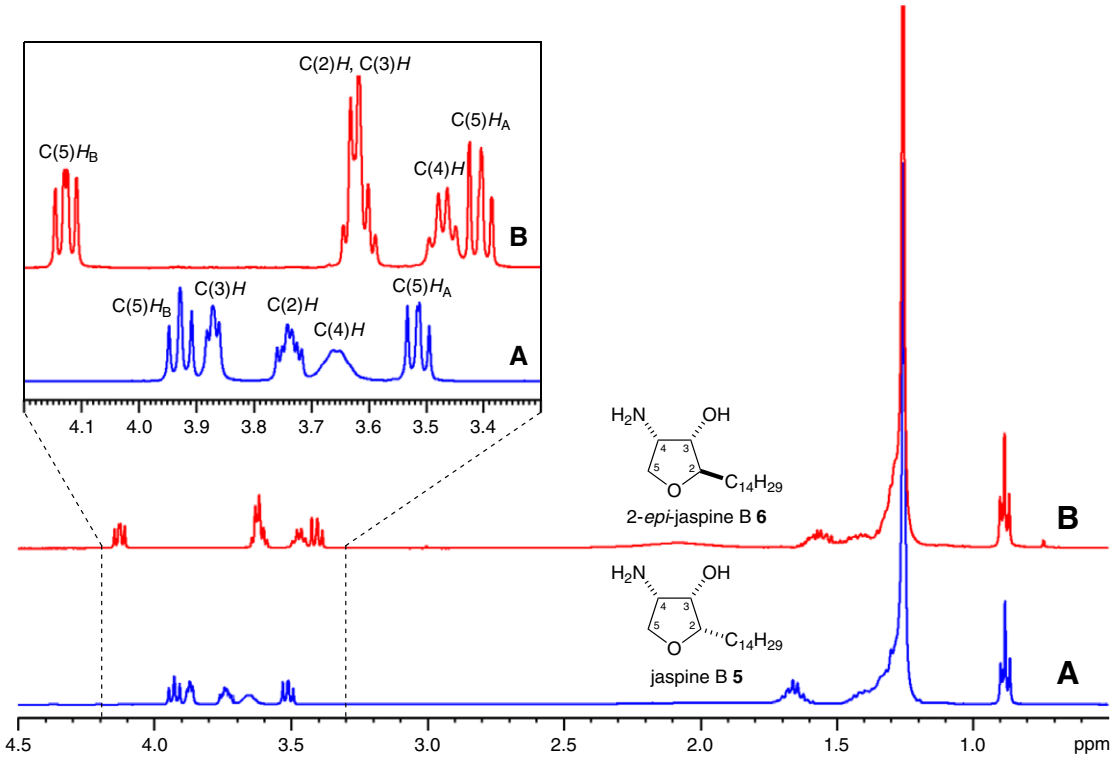


Figure 4. 400 MHz ^{1}H NMR spectra for (**A**) jaspine B **5** and (**B**) 2-*epi*-jaspine B **6** in $CDCl_3$.

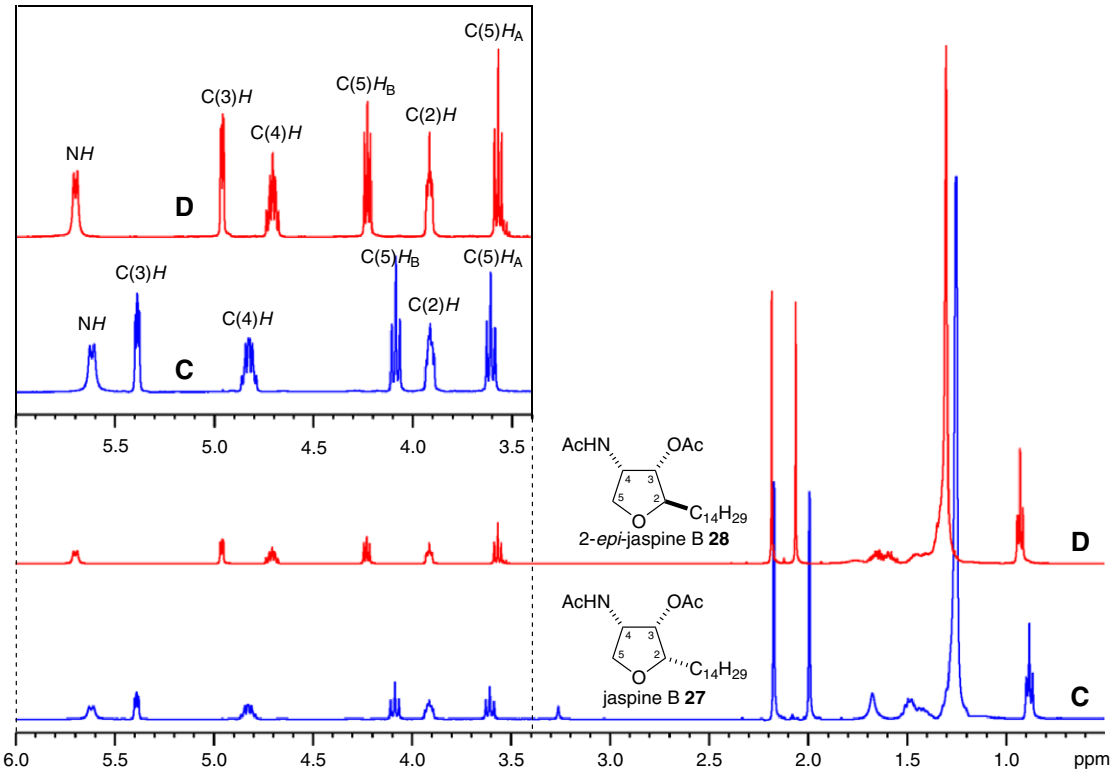


Figure 5. 400 MHz ^{1}H NMR spectra for (**C**) *N*,*O*-diacetyl jaspine B **27** and (**D**) *N*,*O*-diacetyl-2-*epi*-jaspine B **28** in $CDCl_3$. [^{1}H NMR NOE studies have determined that for *N*,*O*-diacetyl jaspine B **27** C(5)H_A is *anti* to the *N*-acetylamino group and for *N*,*O*-diacetyl-2-*epi*-jaspine B **28** C(5)H_A is *syn* to the *N*-acetylamino group.]

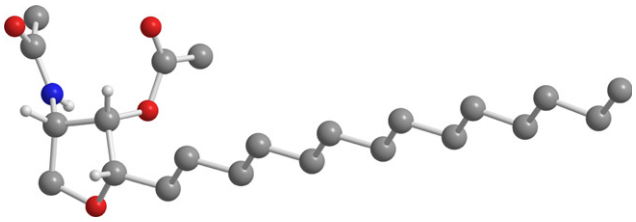
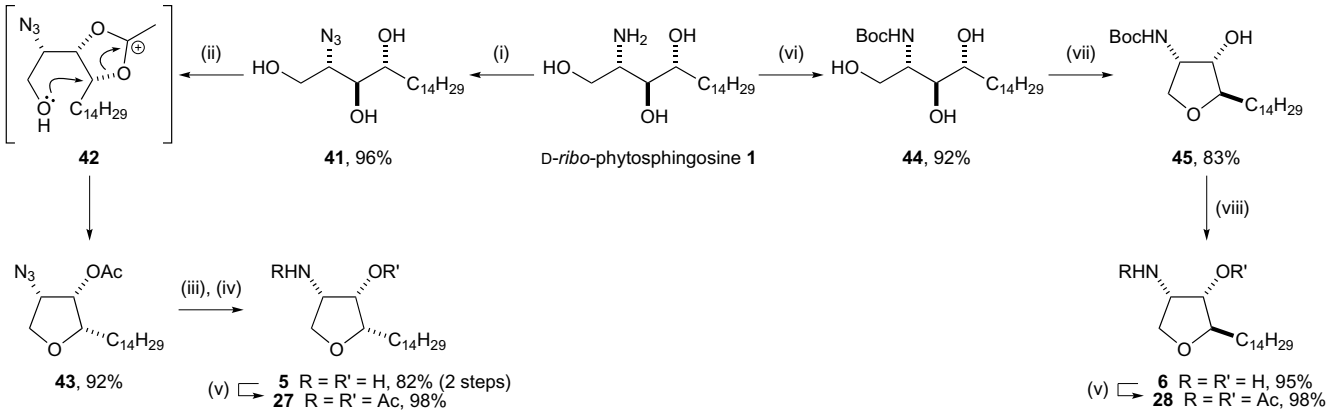


Figure 6. Chem 3 D representation of the X-ray crystal structure of *N*,*O*-diacetyl jaspine B **27** (some H atoms omitted for clarity; CCDC deposition number 616170). A crystal structure of *N*,*O*-diacetyl jaspine B **27** has also been reported by Ramana et al. (CCDC deposition number 617243).[16]

4.2. Enantiospecific syntheses of jaspine B

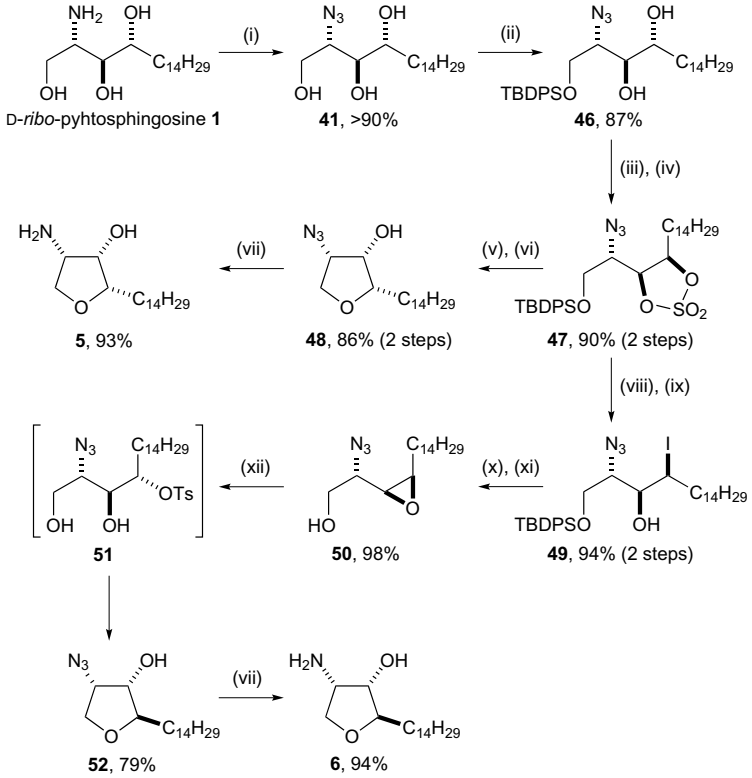
In addition to our synthesis, 13 independent syntheses of jaspine B **5** have been reported. A number of enantiospecific syntheses were first to appear following the isolation of jaspine B **5**, with asymmetric approaches being disclosed later. Several different chiral pool starting materials have been used in the enantiospecific syntheses, including D-*ribo*-phytosphingosine,[12] L-serine,[13] D-xylose,[15] D-glucose,[16] D-galactose,[14] D-tartaric acid[18] and (*R*)-glycidol.[17] The strategies employed have used both starting materials that contain the desired stereochemistry at the N-bearing centre, such as D-*ribo*-phytosphingosine and L-serine, or installed this stereochemistry at a later stage in the synthesis, for example, by manipulation of a carbohydrate derivative.[14–16] This is most frequently achieved by S_N2 displacement with a nitrogen nucleophile (e.g., azide),[14–16,18,20b] although directed C–H amination has also been employed.[20a]

4.2.1. Manipulation of D-*ribo*-phytosphingosine: stereodivergent syntheses to both jaspine B and 2-*epi*-jaspine B. Overkleeft et al. have reported the synthesis of jaspine B **5** and 2-*epi*-jaspine B **6**, and their derivatisation to the corresponding *N*,*O*-diacetyl derivatives **27** and **28**, all based upon manipulation of D-*ribo*-phytosphingosine **1**. Thus, treatment of **1** with triflic azide (TfN_3) resulted in efficient diazotransfer to produce azide **41** in 96% yield. Subsequent Lewis acid-promoted cyclisation upon treatment with BF_3 and trimethylorthoacetate (TMOA) gave tetrahydrofuran derivative **43** in 92% yield, presumably via oxonium ion **42**. Removal of the acetate group was followed by Staudinger reduction of the azide group to give jaspine B **5** in 82% yield over the two steps (Scheme 5). The synthesis of 2-*epi*-jaspine B **6** from **1** was achieved via initial *N*-Boc protection, followed by selective tosylation of the primary C(1)-hydroxyl and concomitant cyclisation to give **45** in 76% yield over two steps, with *N*-Boc deprotection giving 2-*epi*-jaspine B **6** in 95% yield. Both jaspine B **5** and 2-*epi*-jaspine B **6** were converted into the corresponding *N*,*O*-diacetyl derivatives **27** and **28** by treatment with Ac_2O and pyridine (98% yield in both cases). Full characterisation data are reported for jaspine B **5**, 2-*epi*-jaspine B **6** and their corresponding *N*,*O*-diacetyl derivatives **27** and **28**: these data are in good agreement with both the data reported by Debitus et al.[11] for **5** and **27**, and the data obtained in our laboratory (Scheme 5).[12a]



Scheme 5. Reagents and conditions: (i) TfN_3, Na_2CO_3, $CuSO_4$, CH_2Cl_2, MeOH, H_2O, rt, 16 h; (ii) TMOA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt, 16 h; (iii) KO^{t}Bu, MeOH; (iv) Me_3P, PhMe/H_2O (24:1), rt, 16 h; (v) Ac_2O, pyridine, rt, 16 h; (vi) $(Boc)_2O$, Et_3N, THF, rt, 30 min; (vii) TsCl, pyridine/CH_2Cl_2 (1:1), rt, 16 h; (viii) TFA, CH_2Cl_2, rt, 3 h.

Kim et al. also report a stereodivergent synthesis of jaspine B **5** and 2-*epi*-jaspine B **6** from D-*ribo*-phytosphingosine **1** via the key cyclic sulfate intermediate **47**.[30] Initial protection of the amino and primary hydroxyl groups of D-*ribo*-phytosphingosine **1** was achieved by sequential treatment with TfN_3 and $CuSO_4$, then *tert*-butyldiphenylsilyl chloride (TBDPSCl) and DMAP to give azido *O*-TBDPS ether **46** in 78% yield. Subsequent treatment with $SOCl_2$ gave the corresponding cyclic sulfite, and oxidation with $RuCl_3$ and $NaIO_4$ afforded cyclic sulfate **47** in 90% overall yield for two steps, from which both jaspine B **5** and 2-*epi*-jaspine B **6** are derived. Desilylative cyclisation of **47** with TBAF resulted in the desired formation of the tetrahydrofuran core to give **48**, with subsequent reduction yielding jaspine B **5** in 56% overall yield from D-*ribo*-phytosphingosine **1**. In order to access 2-*epi*-jaspine B **6**, Kim et al. report the regioselective ring-opening of cyclic sulfate intermediate **47** with iodide, followed by acid-catalysed hydrolysis which is reported to give iodo alcohol **49** in 94% yield. Treatment of **49** with K_2CO_3 in MeOH followed by TBAF afforded epoxy alcohol **50** in 98% yield for two steps. Subsequent treatment of **50** with a catalytic amount

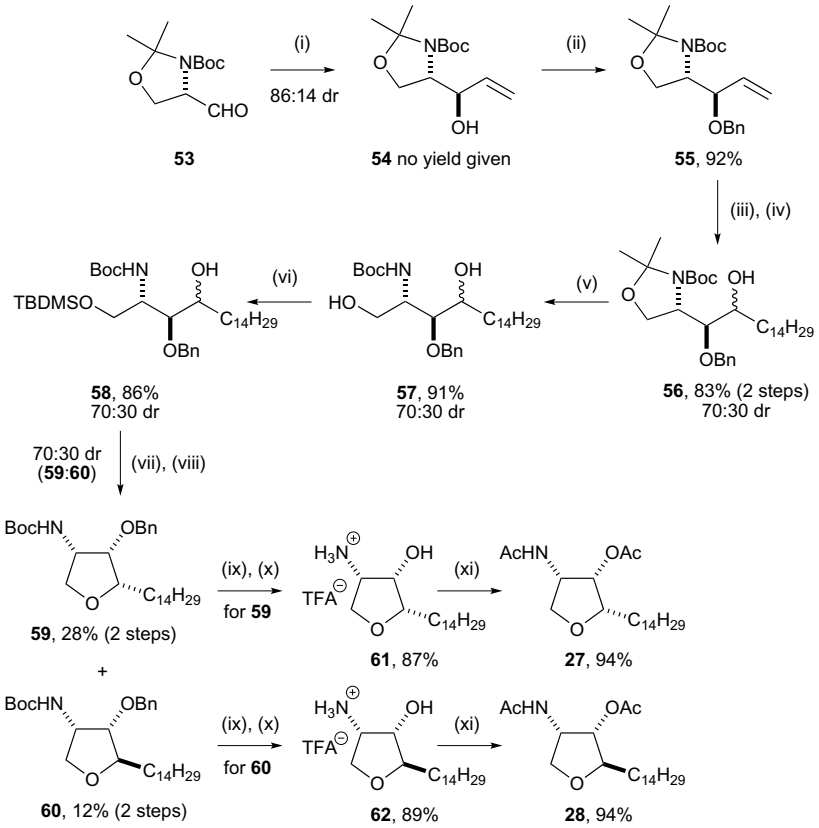


Scheme 6. Reagents and conditions: (i) TfN_3, K_2CO_3, $CuSO_4$, MeOH/H_2O/CH_2Cl_2, rt, 3 h; (ii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 24 h; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 30 min; (iv) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4/MeCN/H_2O, rt, 2 h; (v) TBAF, THF, rt, 1 h; (vi) H_2SO_4/H_2O, THF, rt, 1 h; (vii) H_2, Pd/C, MeOH, rt, 3 h; (viii) Bu_4NI, THF, 40 °C, 1 h; (ix) H_2SO_4, H_2O, THF; (x) K_2CO_3, MeOH, rt, 2 h; (xi) TBAF, THF, rt, 2 h; (xii) TsOH, PhMe, reflux, 12 h.

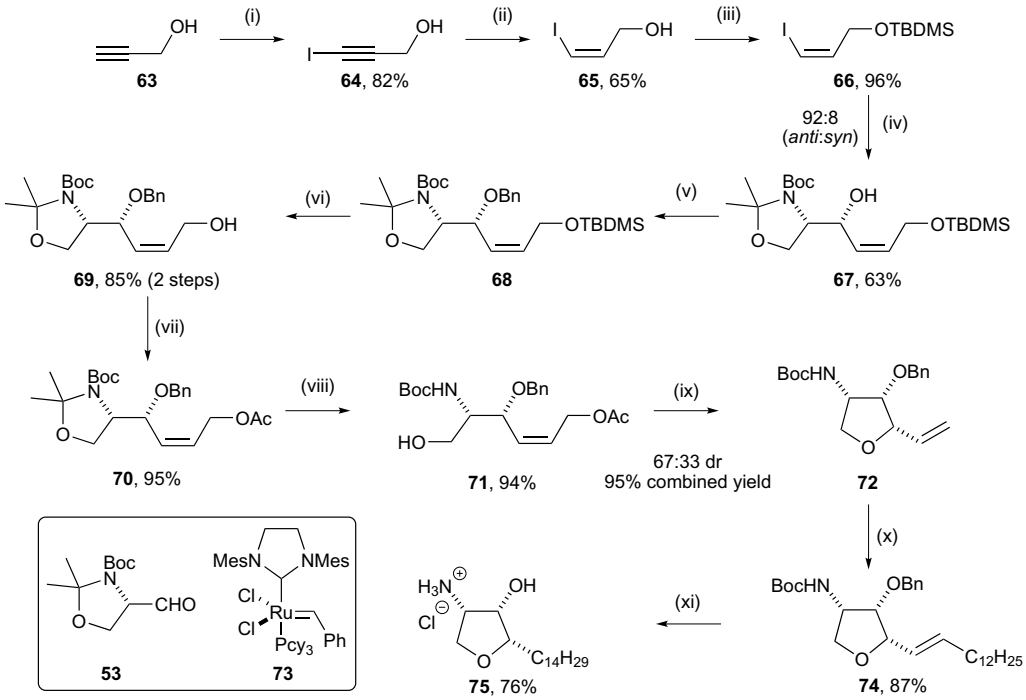
of *p*-toluenesulfonic acid (TsOH) at reflux promoted cyclisation to tetrahydrofuran derivative **52** in 79% yield, with hydrogenation giving 2-*epi*-jaspine B **6** in 94% yield (48% yield in ten steps from D-*ribo*-phytosphingosine **1**). The mechanism of cyclisation to **52** is proposed by the authors to proceed via an unusual regioselective epoxide ring-opening[31] with TsOH to give β-hydroxytosylate **51**, which cyclises in situ to give **52**. In support of this mechanism, the authors report the isolation of β-hydroxytosylate **51** upon treatment of **50** with stoichiometric TsOH at rt (Scheme 6).[12b]

4.2.2. Manipulation of L-serine derivatives. The synthesis of jaspine B **5** reported by Rao and co-workers in 2005 used L-serine derived Garner's aldehyde **53** as the source of chirality.[13a] Addition of vinylmagnesium bromide to aldehyde **53** gave a separable 86:14 mixture of diastereoisomeric alcohols in accordance with the well-known modified Felkin–Ahn selectivity for addition.[32] The major diastereoisomer **54** was protected as the corresponding benzyl ether to give **55** in 92% isolated yield. Ozonolysis of **55** was followed by addition of tetradecylmagnesium bromide to give an inseparable 70:30 mixture of the diastereoisomeric alcohols **56** in 83% yield over two steps. Deprotection of the acetonide protecting group gave a 70:30 mixture of protected D-*ribo*- and D-*lyxo*-phytospingosine derivatives **57** in 91% yield, with subsequent selective silylation of the primary hydroxy with TBDMSCl giving a 70:30 mixture of diastereoisomeric *O*-silyl protected amino alcohols **58** in 86% yield. Mesylation followed by treatment of the corresponding mesylates with TBAF promoted desilylation and concomitant cyclisation to a separable 70:30 mixture of tetrahydrofurans, from which the all-*cis* diastereoisomer **59** was isolated in 28% yield and its C(2)-epimer **60** was isolated in 12% yield. Subsequent debenzylation and diacetylation of **59** and **60** gave *N*,*O*-diacetyl jaspine B **27** in 82% yield and *N*,*O*-diacetyl 2-*epi*-jaspine B **28** in 84% yield, respectively (Scheme 7).

Passiniemi and Koskinen report a synthesis of jaspine B hydrochloride **75** using L-serine-derived Garner's aldehyde **53** as the source of chirality, with Pd(0)-mediated cyclisation and Ru-mediated cross-metathesis reactions as the key steps in the synthesis. Iodide **66** was coupled with Garner's aldehyde **53** by treatment with BuLi and *N*,*N*′-dimethyl-*N*,*N*′-propylene urea (DMPU) to give a separable 92:8 mixture of diastereoisomers, with the major isomer **67** isolated in 63% yield. Subsequent benzylation, *O*-TBDMS deprotection and acetylation gave acetate **70** in 81% overall yield over three steps. Hydrolysis of the *N*,*O*-acetal followed by Pd(0)-mediated intramolecular 1,5-cyclisation[33] gave a separable 67:33 mixture of diastereoisomeric tetrahydrofuran derivatives in 95% combined yield. The all-*cis* isomer **72** was then coupled with 1-tetradecene (10 equiv) via a



Scheme 7. Reagents and conditions: (i) vinylmagnesium bromide, THF, 0 °C to rt, 12 h; (ii) BnBr, THF, NaH, 0 °C to rt, 12 h; (iii) O_3, CH_2Cl_2, −78 °C 1 h, Me_2S; (iv) $C_{14}H_{29}MgBr$, THF, 12 h, rt; (v) AcOH, 0 °C to rt, 12 h; (vi) TBDMSCl, imidazole, CH_2Cl_2, DMAP, 0 °C to rt, 12 h; (vii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt 12 h; (viii) TBAF, THF, rt, 2 h; (ix) Na, NH_3, THF, −78 °C, 30 min; (x) TFA:CH_2Cl_2 (1:1), rt, 6 h; (xi) Et_3N, Ac_2O, CH_2Cl_2, 0 °C to rt, 4 h.

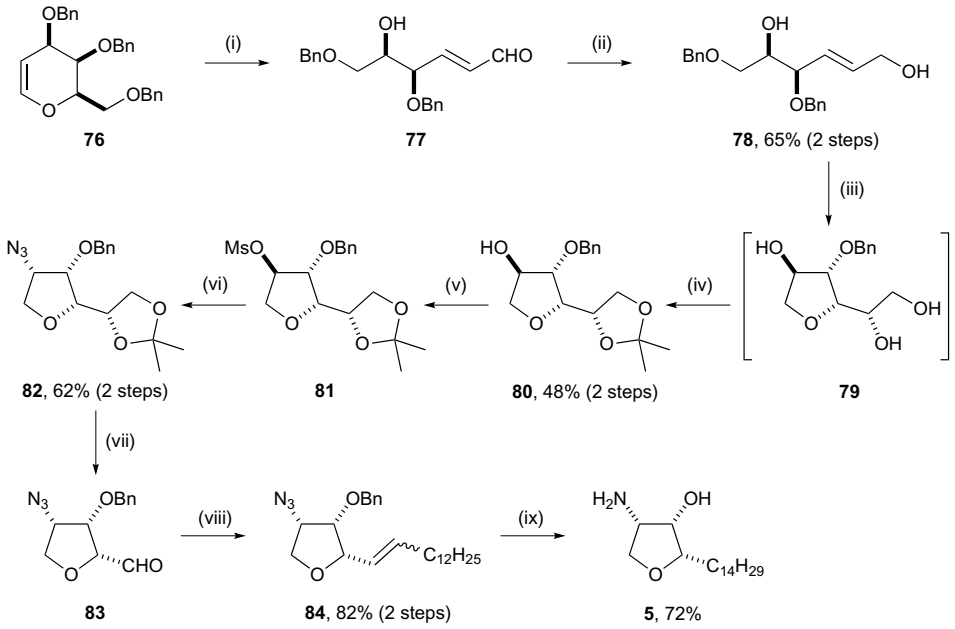


Scheme 8. Reagents and conditions: (i) I_2, KOH, MeOH; (ii) $KO_2CN{=}NCO_2K$, AcOH, MeOH; (iii) TBDMSCl, imidazole, DMF; (iv) BuLi, DMPU, PhMe, −78 °C then **53**, PhMe, −95 °C; (v) BnBr, TBAI, NaH, THF, 0 °C then Δ; (vi) TBAF, CH_2Cl_2, rt; (vii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; (viii) $FeCl_3$–SiO_2, $CHCl_3$, rt; (ix) $Pd(PPh_3)_4$, PPh_3, THF, 55 °C; (x) Grubbs II **73**, 1-tetradecene, CH_2Cl_2, 40 °C; (xi) H_2, $Pd(OH)_2$, MeOH/EtOAc (1:1), rt then HCl, MeOH/EtOAc (1:1).

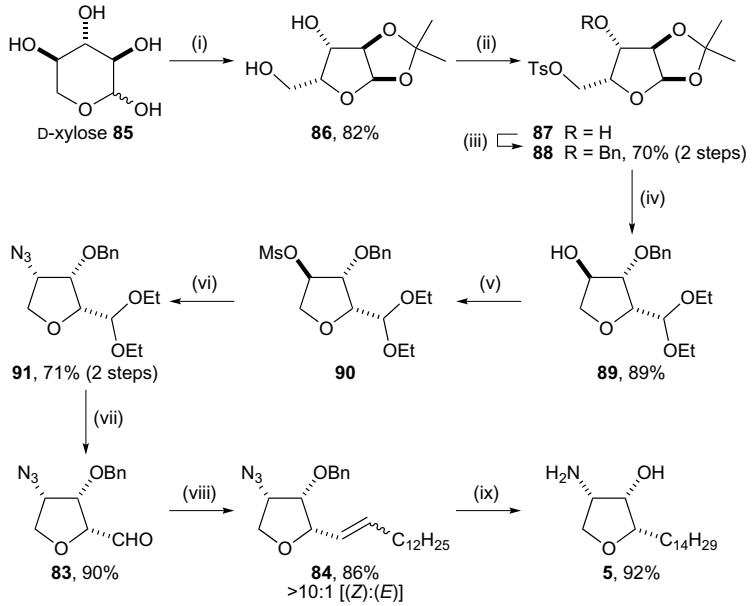
cross-metathesis reaction with Grubbs II **73** to give **74** as the only diastereoisomer in 87% yield. Tandem hydrogenation/hydrogenolysis of **74** with $Pd(OH)_2/C$ under H_2, followed by treatment with HCl gas was reported to afford jaspine B hydrochloride **75** in 76% yield (Scheme 8).[13c]

4.2.3. Manipulation of carbohydrate derivatives. Several carbohydrate starting materials have also been employed for enantiospecific syntheses of jaspine B **5**. Shaw et al. have reported a synthesis of jaspine B **5** using D-galactose as the source of chirality. Initial treatment of tri-*O*-benzyl-D-galactal **76** under Perlin hydrolysis conditions gave α,β-unsaturated aldehyde **77**, which was immediately reduced under Luche conditions to afford allylic alcohol **78** in 65% yield over two steps. Allylic alcohol **78** was then treated under Sharpless asymmetric epoxidation conditions with (+)-diethyl tartrate [(+)-DET] to generate diol **79**, via an intramolecular asymmetric ring-opening process,[34] with subsequent isopropylidene protection giving tetrahydrofuran derivative **80** in 48% yield over two steps.[35] Mesylation of **80** followed by S_N2 displacement with NaN_3 gave azide **82** in 62% yield. Hydrolysis of the acetonide functionality within **82** and periodate cleavage of the resultant diol was followed by Wittig olefination to give **84** as a mixture of geometic isomers, in 82% yield. Global reduction was then achieved via transfer hydrogenation with HCO_2NH_4 in refluxing MeOH to yield jaspine B **5** in 72% yield (Scheme 9).[14]

Du and co-workers initially communicated their synthesis of jaspine B **5** in 2006 in which D-xylose **85** was protected as acetal **86**, regioselectively tosylated on the primary hydroxyl group and benzylated with benzyl trichloroacetimidate and trimethylsilyltriflate (TMSOTf) to give tosylate **88** in 57% overall yield for three steps. Subsequent treatment with HCl in EtOH gave **89**, then mesylation and exposure to NaN_3 generated tetrahydrofuran derivative **91** in 63% yield. Hydrolysis of **91** with aqueous TFA afforded aldehyde **83**, which was then subjected to Wittig olefination giving an inseparable mixture of (*E*)- and (*Z*)-isomers of the corresponding olefin **84** in 77% yield. Finally, **84** was fully reduced under hydrogenation conditions to reportedly give jaspine B **5** in 92% yield as the free base, although the data quoted actually correspond to those of jaspine B TFA salt **61** (Scheme 10).[15a] Subsequently, an improved and scaleable synthesis was reported by Du et al., also starting from D-xylose **85**.[15b] In this approach, protected D-xylose derivative **92** was treated with $NaIO_4$ to generate aldehyde **93**, which was immediately subjected to a Wittig reaction to produce **94** in 82% yield over two steps. Iodine-promoted cyclofunctionalisation/debenzylation of **94** afforded iodide **95**,[35] and subsequent oxidation of the iodomethyl group with DMSO followed by treatment with MsCl gave mesylate **96** in 74% yield over two steps from **95**. Wittig olefination of **96** resulted in the generation of an inseparable mixture of (*E*)- and (*Z*)-isomers **97**, which upon treatment with NaN_3 gave **84** in 72% yield over two steps (Scheme 11). Subsequent elaboration of **84** to jaspine B TFA salt **61** was reported to be directly analogous to the previous synthesis, affording jaspine B TFA salt **61** in 95% yield (Scheme 10). The ^1H and ^{13}C NMR spectroscopic data reported in this article (for jaspine B TFA salt **61**) are in excellent agreement with those reported by Higa et al. for the TFA salt of the natural product.[5]

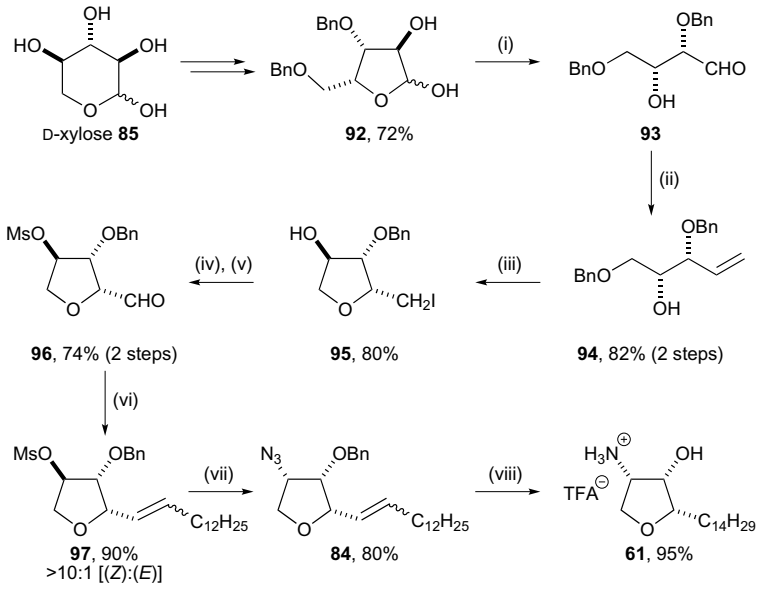


Scheme 9. Reagents and conditions: (i) $HgSO_4$ (cat.), H_2SO_4 (0.01 M, aq), 1,4-dioxane, 0 °C to rt, 8 h; (ii) $NaBH_4$, (0.5 equiv), $CeCl_3{\cdot}7H_2O$ (1.0 equiv), EtOH, 0 °C to rt, 3 h; (iii) $Ti(O^iPr)_4$ (1.0 equiv), (+)-DET (1.2 equiv), $^tBuO_2H$ (2.0 equiv), 4 Å MS, CH_2Cl_2, −25 °C to 0 °C, 2.5 h (iv) satd citric acid in acetone, 2 h; (v) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1.5 h; (vi) NaN_3, Bu_4NCl (cat.), DMF, 120 °C, 3 days; (vii) H_5IO_6 (1.3 equiv), EtOAc, rt, 3 h; (viii) $[C_{13}H_{27}PPh_3]^+[Br]^-$, BuLi, THF, −78 °C; (ix) HCO_2NH_4, MeOH, Pd/C, Δ, 18 h.



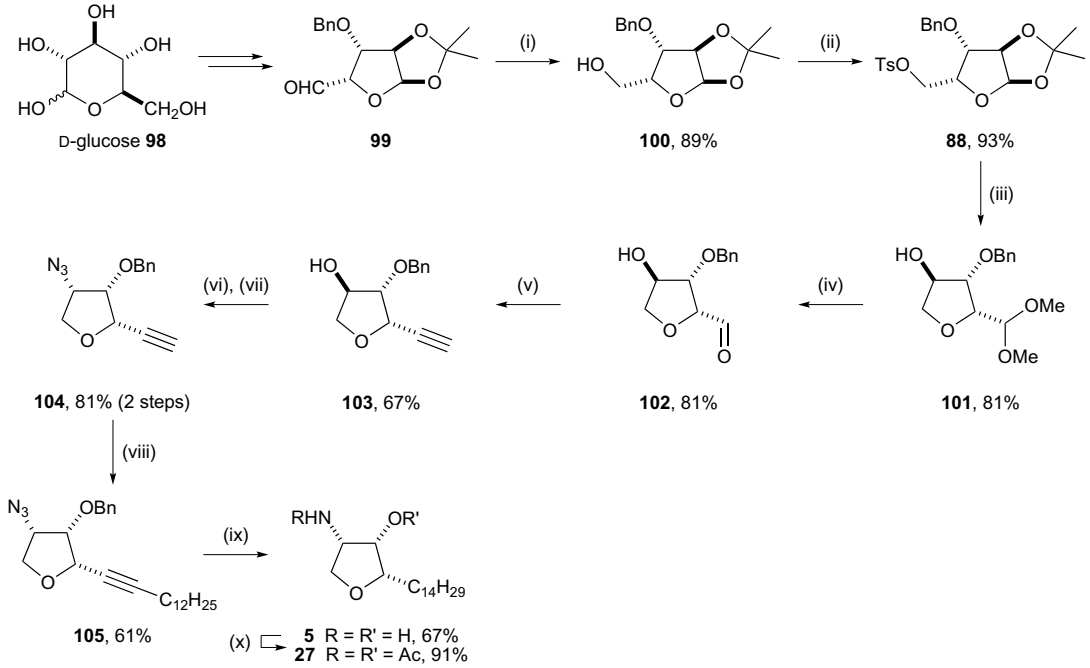
Scheme 10. Reagents and conditions: (i) acetone, H_2SO_4 (concd), then Na_2CO_3; (ii) tosylimidazolide, MeOTf, *N*-methylimidazole, THF; (iii) benzyl trichloroacetimidate, TMSOTf (1 mol %), CH_2Cl_2, −40 °C; (iv) HCl (5% in EtOH, v/v), Δ, 3 h; (v) MsCl, pyridine, rt, 4 h; (vi) NaN_3, NH_4Cl, DMF, 120 °C, 20 h; (vii) TFA (50% aq), CH_2Cl_2, rt, 30 min; (viii) $[C_{13}H_{27}PPh_3]^+[Br]^-$, BuLi, THF, −40 °C; (ix) H_2, $Pd(OH)_2/C$, MeOH/EtOAc, 5 h.

Ramana et al. have reported a stereodivergent synthesis of jaspine B **5** and *ent*-jaspine B *ent*-**5** starting from D-glucose **98**,[16] in a directly analogous fashion to that reported by Du and co-workers.[15a] Conversion of D-glucose **98** to aldehyde **99** (according to a literature procedure)[36] was followed by reduction with $NaBH_4$ and treatment with TsCl to give tosylate **88** in 83% yield (over two steps from aldehyde **99**). Subsequent acid-mediated acetonide deprotection with concomitant cyclisation gave dimethylacetal **101** in 81% yield. Acid catalysed hydrolysis gave aldehyde **102**, which was then subjected to Ohira–Bestmann alkynylation to afford alkynol **103** in 54% yield. Conversion of **103** to the



Scheme 11. Reagents and conditions: (i) $NaIO_4$, MeOH, H_2O; (ii) $[CH_3PPh_3]^+[Br]^-$, BuLi, THF, −40°C to rt; (iii) I_2, $NaHCO_3$, MeCN; (iv) $NaHCO_3$, DMSO, 150°C, 6 min; (v) MsCl, pyridine, rt, 30 min; (iv) $[C_{13}H_{27}PPh_3]^+[Br]^-$, BuLi, THF, −40 °C to rt; (vii) NaN_3, NH_4Cl, DMF, 120 °C, 20 h; (viii) Pd/C, H_2, MeOH, TFA, 5 h.

corresponding azidoalkyne **104** was achieved by treatment with triflic anhydride (Tf_2O) in pyridine, followed by reaction with LiN_3 in DMF to give **104** in 81% yield over two steps. Alkylation of the terminal acetylene **104** with BuLi, hexamethylphosphoramide (HMPA) and $C_{12}H_{25}Br$ gave **105**, which was reduced under transfer hydrogenolysis conditions to give jaspine B **5** in 41% yield over two steps. Whilst no data are reported for the natural product, full characterisation data for the *N*,*O*-diacatate derivative **27**, including X-ray crystal structure data, are given (Scheme 12). Aldehyde **99** was also converted into *ent*-jaspine B *ent*-**5** by first subjecting it to Ohira–Bestmann alkynylation

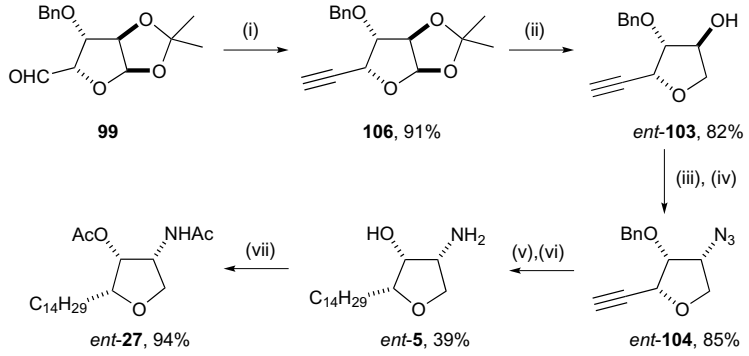


Scheme 12. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C, 2 h; (ii) TsCl, pyridine, DMAP, CH_2Cl_2, 5 h; (iii) TsOH, MeOH, Δ, 6 h; (iv) H_2SO_4 (2.0 M, aq), AcOH (50% aq), 9 °C, 2 h; (v) $(MeO)_2P(O)C(N_2)COCH_3$, MeOH, K_2CO_3, rt, 8 h; (vi) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 6 h; (vii) LiN_3, DMF, rt, 12 h; (viii) BuLi, THF/HMPA (7:1), $C_{12}H_{25}Br$, −78 °C to −40 °C, 1 h; (ix) Pd/C (10% w/w), HCO_2NH_4, MeOH, Δ, 10 h; (x) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 6 h.

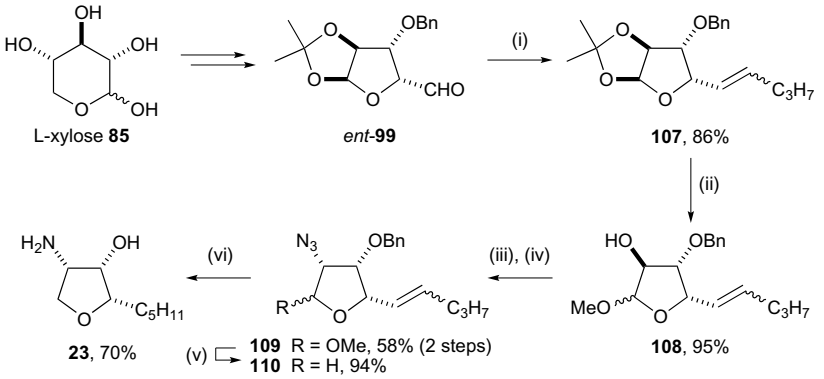
to give **106** and then reductive deketalisation, using excess triethylsilane in the presence of $BF_3{\cdot}Et_2O$, to give *ent*-**103** in 75% yield over two steps. The subsequent steps in the synthesis are directly analogous to that of the natural product with final diacetylation giving *ent*-*N*,*O*-diacetyl jaspine B *ent*-**27** in 31% overall yield in five steps from *ent*-**103** (Scheme 13).

Chandrasekhar et al. have published a synthesis of a 'truncated' version of jaspine B with a C_5H_{11} side chain **23**,[21] based upon manipulation of L-xylose-derived aldehyde *ent*-**99**.[37] Aldehyde *ent*-**99** was subjected to Wittig olefination with $[C_4H_9PPh_3]^+[Br]^-$, hydrolysis and in situ formation of the methyl glycoside to give **108** in 82% yield over two steps. Activation of the hydroxyl group as the corresponding imidazole sulfonate ester allowed S_N2-displacement with NaN_3 to give **109** in 58% yield. Subsequent reduction of **109** with Et_3SiH promoted by BF_3, followed by hydrogenation gave the 'truncated' version of the natural product **23** in 66% yield (Scheme 14). The truncated side chain has little effect on the δ_H/δ_C signals in the ^1H and ^{13}C NMR spectra for the resonances associated with the tetrahydrofuran core and, crucially, the highest field signal is at 3.85–3.95 ppm ($\delta_H < 4.0$ ppm for all ring protons in $CDCl_3$), which is in excellent agreement with an all-*cis* arrangement.

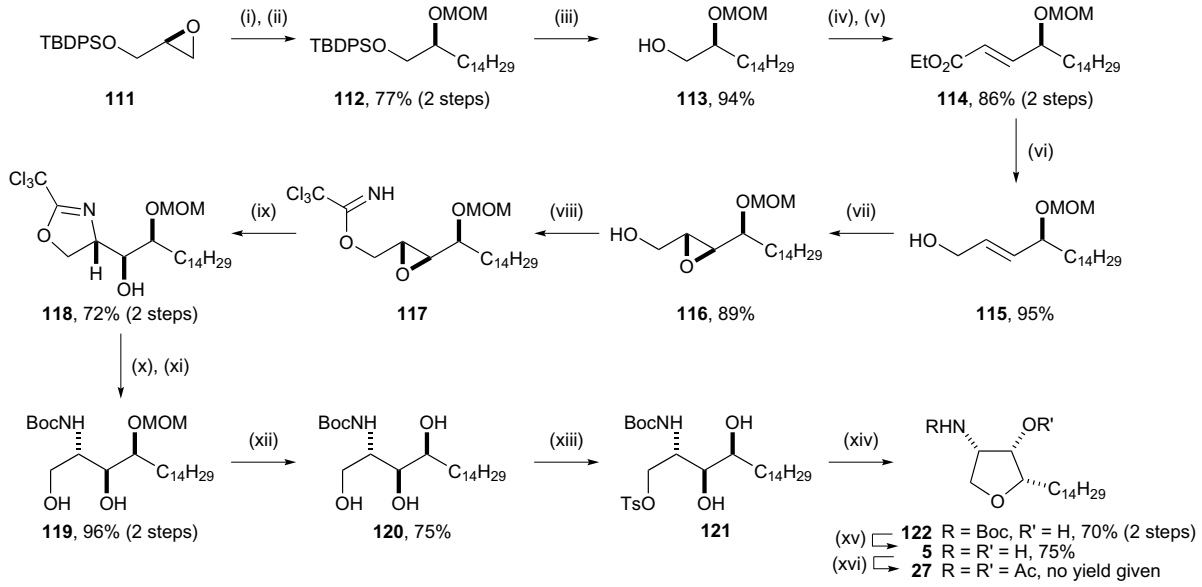
4.2.4. Syntheses based on manipulation of other chiral pool starting materials. In 2006, Marco et al. reported an enantiospecific synthesis of jaspine B **5** from (*R*)-glycidol. *O*-TBDPS protected (*R*)-glycidol **111** was initially treated with tridecylmagnesium bromide in the presence of CuI to afford the corresponding alcohol, which was then protected as its *O*-methoxymethyl (*O*-MOM) derivative **112**. Sequential desilylation, Swern oxidation and olefination then gave α,β-unsaturated ester (*E*)-**114** in 81% yield over three steps. Ester reduction of **114** with DIBAL-H gave allylic alcohol **115**, which was treated under Sharpless asymmetric epoxidation conditions, with (−)-DET, to provide epoxy alcohol **116** in 85% yield.[35] Epoxy alcohol **116** was then treated with trichloroacetonitrile in the presence of DBU to give imino ester derivative **117**, which was then reacted with Et_2AlCl to generate oxazoline **118** in 72% yield. Subsequent hydrolysis and *N*-Boc protection gave diol **119**. Removal of the *O*-MOM group was achieved with TMSBr to give triol **120**, which was treated with TsCl, followed by K_2CO_3 in MeOH to induce cyclisation to give tetrahydrofuran derivative **122** in 50% yield over five steps. *N*-Boc Deprotection of **122** with TFA and subsequent basification with NaOH then gave jaspine B **5** in 75% yield. Full characterisation data for jaspine B **5** and the *N*,*O*-diacetyl derivative **27**, which was prepared by



Scheme 13. Reagents and conditions: (i) $(MeO)_2P(O)C(N_2)COCH_3$, MeOH, K_2CO_3, rt, 8 h; (ii) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −20 °C to rt, 6 h; (iii) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 6 h; (iv) LiN_3, DMF, rt, 12 h; (v) BuLi, THF/HMPA (7:1), $C_{12}H_{25}Br$, −78 °C to −40 °C, 1 h; (vi) Pd/C (10% w/w), HCO_2NH_4, MeOH, Δ, 10 h; (vii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 6 h.



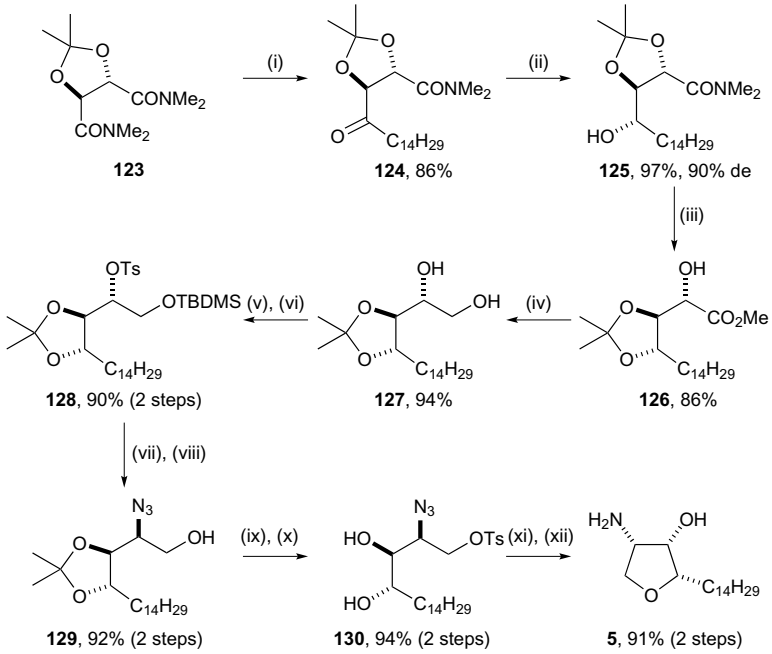
Scheme 14. Reagents and conditions: (i) $[C_4H_9PPh_3]^+[Br]^-$, BuLi, THF/HMPA, −40 °C, 4 h; (ii) AcCl, MeOH, 60 °C, 8 h; (iii) SO_2Im_2, NaH, DMF, −40 °C, 3 h; (iv) NaN_3, Bu_4NCl, DMF, 110 °C, 12 h; (v) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, 0 °C to rt, 2 h; (vi) Pd/C, H_2, MeOH, rt, 6 h.



Scheme 15. Reagents and conditions: (i) $C_{13}H_{27}MgBr$, CuI, THF, −10 to 0 °C; (ii) MOMCl, EtN^iPr_2, CH_2Cl_2, rt, 24 h; (iii) TBAF, THF, rt, 3 h; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −46 °C, 3 h; (v) $(^iPrO)_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt; (vi) DIBAL-H, hexane, 0 °C, 2.5 h; (vii) $^tBuO_2H$, (−)-DET, $Ti(O^iPr)_4$, CH_2Cl_2, −20 °C, 24 h; (viii) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 30 min; (ix) Et_2AlCl, CH_2Cl_2, 0 °C to rt, 5 h; (x) HCl (1.0 M, aq), THF, rt, 5 h; (xi) Boc_2O, $NaHCO_3$, THF, rt, 16 h; (xii) TMSBr, CH_2Cl_2, −78 °C, 30 min; (xiii) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 20 min; (xiv) K_2CO_3, MeOH, rt, 16 h; (xv) TFA, CH_2Cl_2, 0 °C to rt, 45 min then NaOH, MeOH, 5 min; (xvi) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 16 h.

treatment of the free base with Ac_2O, Et_3N and DMAP, are reported (Scheme 15).[17]

Chandrakumar and Prasad have reported a synthesis of jaspine B **5** starting from D-tartaric acid-derived bisdimethylamide **123**. Addition of tetradecylmagnesium bromide to bisdimethylamide **123** gave keto amide **124** in 86% yield, and stereoselective reduction of ketone **124** under Luche conditions furnished a mixture of diastereomeric alcohols (90% de) with **125** as the major diastereoisomer. Subsequent reaction of this mixture with excess 2,2-dimethoxypropane and TsOH gave a separable mixture of



Scheme 16. Reagents and conditions: (i) $C_{14}H_{29}MgBr$, THF, −15 °C, 30 min; (ii) $NaBH_4$, $CeCl_3$, MeOH, −15 °C, 2 h; (iii) 2,2-dimethoxypropane, TsOH, C_6H_6, Δ, 12 h; (iv) $NaBH_4$, MeOH, −15 °C to rt, 3 h; (v) TBDMSCl, imidazole, DMF, rt, 12 h; (vi) TsCl, DMAP, CH_2Cl_2, rt, 14 h; (vii) NaN_3, DMF, 100 °C, 12 h; (viii) TBAF, THF, 0 °C to rt, 1 h; (ix) TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 5 h; (x) $FeCl_3{\cdot}6H_2O$, CH_2Cl_2, rt, 8 h; (xi) K_2CO_3, MeOH, 0 °C to rt, 4 h; (xii) H_2, Pd/C, MeOH, CH_2Cl_2, rt, 3 h.

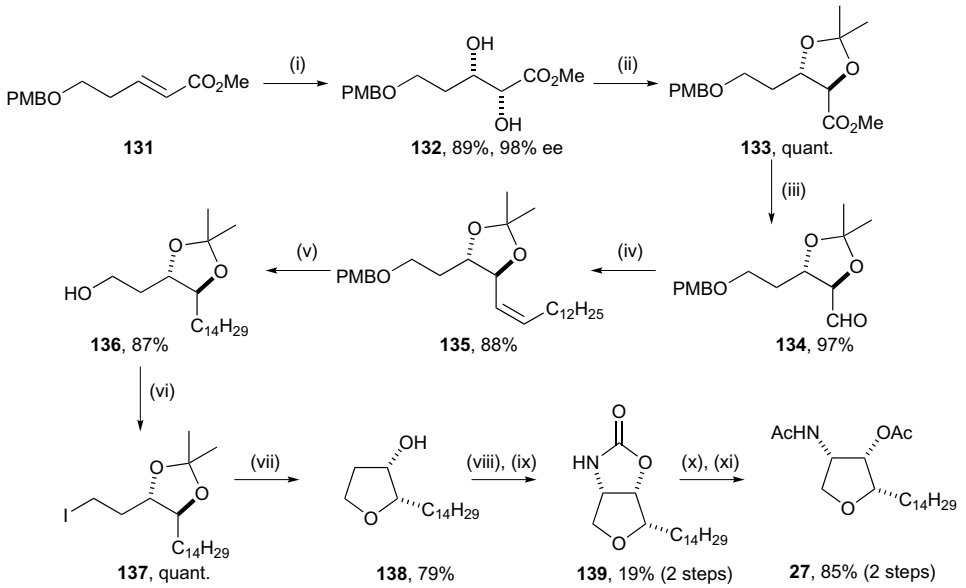
diastereoisomeric alcohols, from which the major diastereoisomer **126** was isolated in 86% yield. Alcohol **126** was reduced with $NaBH_4$ to afford diol **127**, which was first treated with TBDMSCl, then TsCl to give **128** in 85% yield (over three steps). Treatment of **128** with NaN_3 gave a mixture of the expected S_N2 displacement product and also resulted in partial desilylation, subsequent treatment with TBAF afforded azohydrin **129** in 92% yield from **128**. Tosylation of **129** followed by acid-promoted acetonide hydrolysis, then treatment with K_2CO_3 in MeOH gave the corresponding tetrahydrofuran derivative in 91% yield. Subsequent azide reduction with Pd/C gave jaspine B **5** in 94% yield (Scheme 16).[18]

4.3. Other asymmetric syntheses of jaspine B

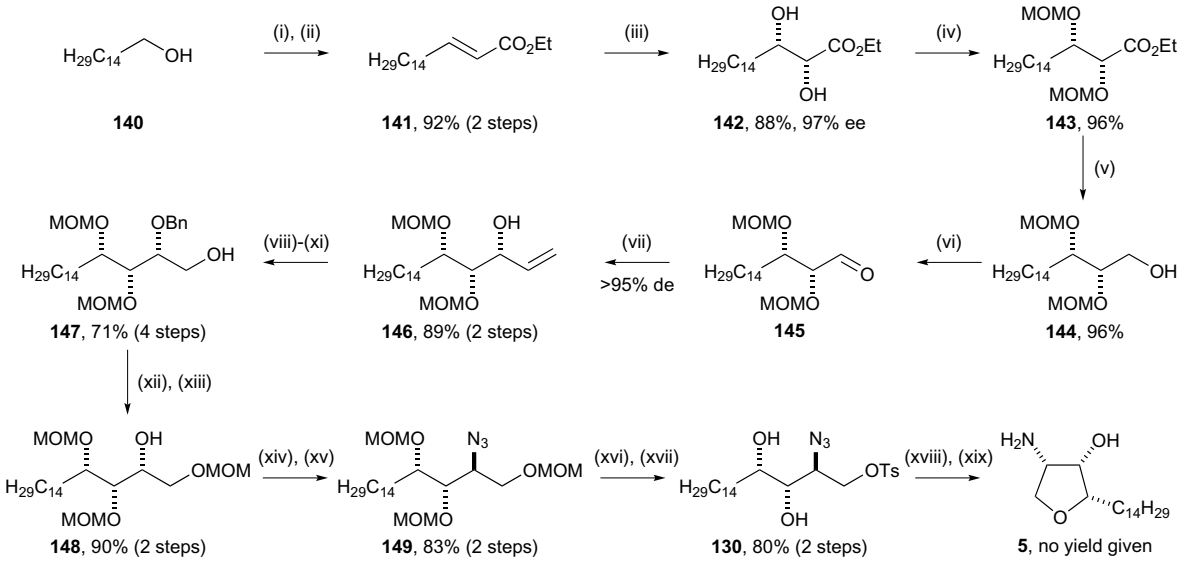
In addition to the syntheses of jaspine B **5** highlighted above, there have also been two further asymmetric syntheses of the natural product, the first of these by Yakura et al. utilises the Sharpless asymmetric dihydroxylation of α,β-unsaturated ester **131** to give diol **132** in 98% ee. Subsequent acetonide protection, reduction with DIBAL-H and Wittig olefination gave **135** as a single diastereoisomer in 85% yield. One-pot removal of the *O*-*p*-methoxybenzyl (*O*-PMB) group and olefin reduction was then achieved under hydrogenation conditions to give **136**, which was treated with I_2 and PPh_3 to afford iodide **137** in 87% yield from olefin **135**. Acid-catalysed deprotection of **137** followed by cyclisation gave tetrahydrofuran **138**. Subsequent treatment with trichloroacetyl isocyanate and Rh-mediated C–H amination gave a mixture of products from which **139** was isolated in 19% yield from **138**. Hydrolysis of **139** with KOH and acetylation with Ac_2O in pyridine gave *N*,*O*-diacetyl jaspine B **27** in 85% yield (Scheme 17).[20a]

Venkatesan and Srinivasan have also reported an asymmetric synthesis of jaspine B **5** which utilises Sharpless asymmetric dihydroxylation and a chelation-controlled vinyl Grignard addition as the key steps in the synthetic strategy. 1-Pentadecanol **140** was subjected to oxidation with pyridinium chlorochromate (PCC), followed by Wittig olefination to give α,β-unsaturated ester **141** in 92% yield. α,β-Unsaturated ester **141** was then treated under Sharpless asymmetric dihydroxylation conditions to give diol **142** in 88% yield and 97% ee. Subsequent *O*-MOM protection, reduction and re-oxidation gave aldehyde **145** which was immediately treated with vinyl magnesium bromide, under chelation control, to give allylic alcohol **146** in >95% de and 89% yield from alcohol **144**. *O*-Benzyl protection of **146**, oxidative cleavage and reduction then gave alcohol **147** in 71% yield over four steps. Subsequent protecting group manipulation, tosylation and azide displacement then gave azide **149** in 75% yield over four steps. Acidic hydrolysis of **149** followed by treatment with TsCl gave tosylate **130** which was reacted according to the procedure outlined by Chandrakumar and Prasad[18] (vide supra) to give jaspine B **5** (Scheme 18).[20b]

The synthesis of another 'truncated' C_8H_{17} side chain analogue **24** is reported by Génisson et al., the synthesis of which is based on Sharpless asymmetric aminohydroxylation of allylic alcohol **150**. Under these conditions, a 70:30 mixture of amino alcohols **151** and **152** is produced; subsequent treatment with methyl chloroformate generated a separable mixture of regioisomeric oxazolidinones **153** and **154**, which were isolated in 60% and 23% yields, respectively; the *cis*-stereochemistry of the major product **153** was established by single crystal X-ray analysis. Oxidation of **153** with Dess–Martin periodinane (DMP) gave aldehyde **155** in 90% yield. The C_8H_{17} side chain was then



Scheme 17. Reagents and conditions: (i) AD-mix-α, BuOH–H_2O, 0 °C, 16 h; (ii) $Me_2C(OMe)_2$, CSA, rt, 12 h; (iii) DIBAL-H, CH_2Cl_2, −80 °C, 1 h; (iv) $[Ph_3PC_{13}H_{27}]^+[Br]^-$, BuLi, THF, −20 °C, 1 h; (v) H_2 (3 atm), Pd/C, EtOAc, rt, 3 h; (vi) I_2, PPh_3, imidazole, CH_2Cl_2, rt, 1 h; (vii) concd HCl, THF, rt, 2.5 h then K_2CO_3, MeOH, rt, 3 h; (viii) $Cl_3CCON{=}C{=}O$, CH_2Cl_2, rt, 1 h then neutral Al_2CO_3; (ix) $Rh_2(OCOCPh_3)_4$ (10 mol %), $PhI(OAc)_2$ (4.2 equiv), MgO (6.9 equiv), C_6H_6, reflux, 13 h; (x) KOH (aq), EtOH, reflux, 3 h; (xi) Ac_2O, pyridine, rt, 12 h.

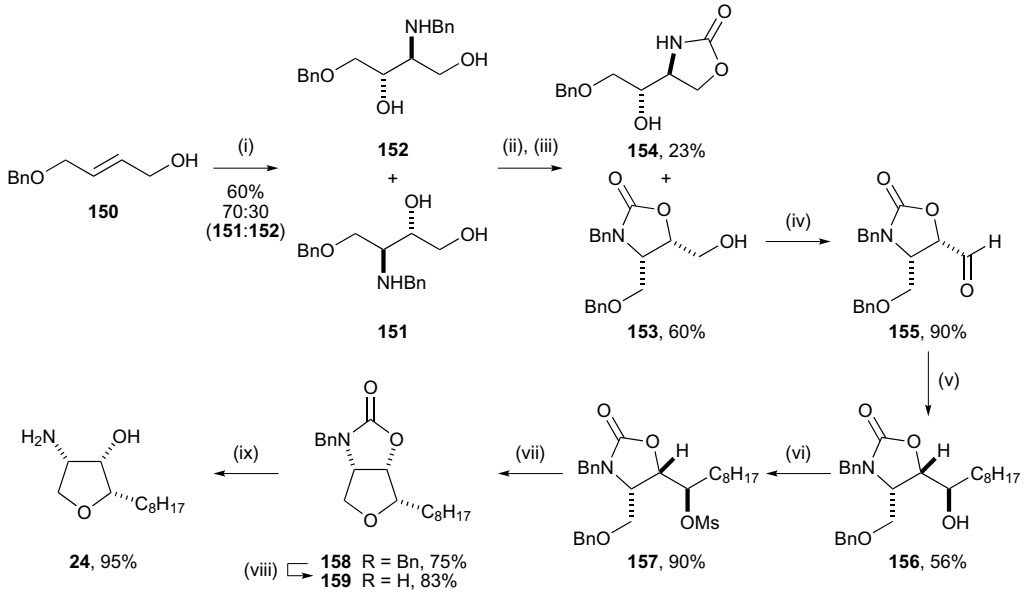


Scheme 18. Reagents and conditions: (i) PCC, CH_2Cl_2, 0 °C, 3 h; (ii) Ph_3PCHCO_2Et, C_6H_6, Δ, 4 h; (iii) $(DHQ)_2PHAL$, K_2CO_3, $K_3[Fe(CN)_6]$, $MeSO_2NH_2$, OsO_4 (0.1 M in PhMe), $^tBuOH/H_2O$ (1:1), 0 °C, 24 h; (iv) MOMCl, CH_2Cl_2, EtN^iPr_2, 0 °C to rt, 16 h; (v) DIBAL-H, CH_2Cl_2, −10 °C, 1 h; (vi) IBX, EtOAc, Δ, 3 h; (vii) vinylmagnesium bromide, $MgBr_2{\cdot}Et_2O$, THF, −78 °C, 45 min; (viii) BnBr, NaH, THF, 0 °C, 4 h; (ix) OsO_4 (0.1 M in PhMe), $^tBuOH/THF/H_2O$ (3:2:1), *N*-methylmorpholine-*N*-oxide (NMO), 16 h; (x) $NaIO_4$, $NaHCO_3$, H_2O, rt, 3 h; (xi) $NaBH_4$, MeOH, 0 °C to rt, 1 h; (xii) MOMCl, CH_2Cl_2, EtN^iPr_2, 0 °C to rt, 6 h; (xiii) H_2, Pd/C, MeOH, rt, 16 h; (xiv) TsCl, CH_2Cl_2, Et_3N, DMAP, 0 °C to rt, 3 h; (xv) NaN_3, DMF, 95 °C, 14 h; (xvi) aq HCl, THF, 0 °C to rt, 5 h; (xvii) TsCl, CH_2Cl_2, DMAP, 0 °C to rt, 4 h; (xviii) K_2CO_3, MeOH, 0 °C to rt, 4 h; (xix) H_2, Pd/C, MeOH, rt, 3 h.

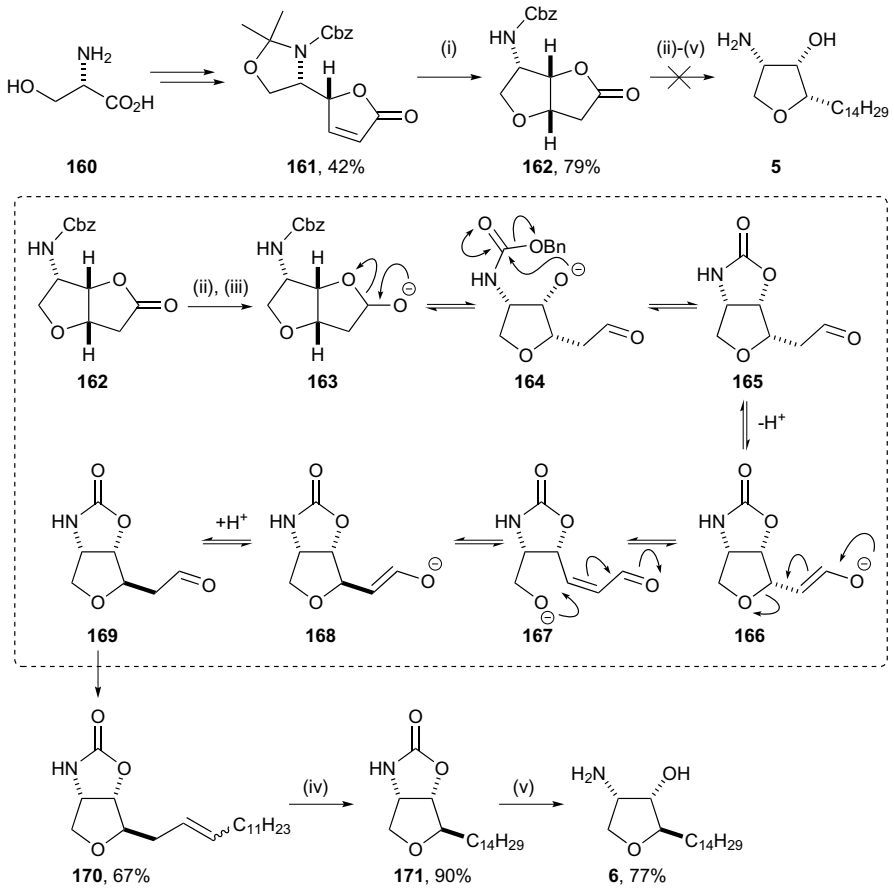
introduced via Grignard addition to aldehyde **155**; mesylation of the resultant alcohol **156** followed by hydrogenolytic O-debenzylation and in situ cyclisation gave tetrahydrofuran derivative **158** in 68% yield. N-Debenzylation of **158** was achieved via Birch reduction, and saponification of the resultant oxazolidinone **159** gave the 'truncated' version of the natural product **24** in 95% yield, with ^1H NMR data ($\delta_H < 4.0$ ppm for all ring protons in $CDCl_3$) supporting an all-*cis* arrangement (Scheme 19).[22]

4.4. Synthesis with inconsistent data

Datta et al. communicated their purported synthesis of jaspine B **5** in 2005;[13b] in this synthesis L-serine **160**



Scheme 19. Reagents and conditions: (i) $Ti(O^iPr)_4$, (−)-DET, $^tBuO_2H$, 4 Å MS, CH_2Cl_2, −23 °C, 3 days then Me_2S, rt, 3 h, then, $Ti(O^iPr)_4$, $BnNH_2$, rt, 1.5 days; (ii) K_2CO_3, MeOCOCl, THF, rt, 18 h; (iii) KOH, MeOH, rt, 5 h; (iv) DMP, CH_2Cl_2, rt, 3 h; (v) $C_8H_{17}MgBr$, $CeCl_3$, THF, −78 °C, 5 h then 0 °C, 1 h; (vi) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1.5 h; (vii) H_2 (10 bar), $Pd(OH)_2$, EtOH, 2 days; (viii) Na/NH_3, THF, −78 °C, 4 h; (ix) KOH, $EtOH/H_2O$, 85 °C, 7 h.



Scheme 20. Reagents and conditions: (i) HCO_2H, CH_2Cl_2, 0 °C then EtOAc, satd aq $NaHCO_3$; (ii) DIBAL-H, −78 °C; (iii) $[Ph_3PC_{12}H_{25}]^+[Br]^-$, BuLi, THF, −78 °C to rt; (iv) Pd/C, H_2, EtOAc, rt; (v) aq KOH, EtOH, Δ.

was converted into butenolide **161**, the synthesis of which had previously been developed in the Datta laboratories.[38] Treatment of **161** with formic acid in dichloromethane enabled deprotection of the acetonide, with subsequent Michael addition of the free hydroxyl group giving *cis*-fused bicycle **162**; the structure of which was supported by X-ray crystallographic analysis of related derivatives.[13b,39] Subsequent elaboration of this compound was reported to furnish jaspine B **5** as the free base in 46% yield over four steps. Unfortunately upon inspection of the spectroscopic data reported by Datta et al., and comparison with the other natural and synthetic samples of jaspine B **5** discussed in this review, it is evident that the data are anomalous and in fact closely resemble those of 2-*epi*-jaspine B **6**; a full comparison of the relevant spectroscopic data is given below. This discrepancy can be accounted for by a retro-Michael/Michael epimerisation pathway upon treatment of bicyclic lactone **162** with DIBAL-H and excess Wittig reagent. Enolate **166**, which is generated under these conditions, may undergo a retro-Michael reaction to generate α,β-unsaturated aldehyde **167**. Recyclisation of the resultant oxyanion species would generate the thermodynamically favoured 2,3-*anti*-aldehyde **168**, which is trapped out as the corresponding olefin **170**. Subsequent hydrogenation of **170** and cleavage of the resultant oxazolidinone **171** with ethanolic KOH afforded 2-*epi*-jaspine B **6** in 77% yield (Scheme 20).

5. Comparison of spectroscopic data

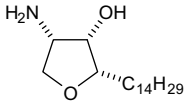
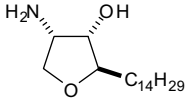
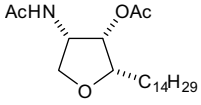
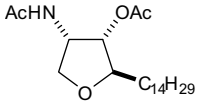
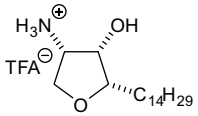
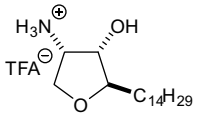
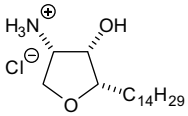
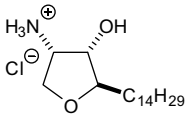
5.1. Specific rotation

A summary of the reported specific rotation data for jaspine B **5**, 2-*epi*-jaspine B **6** (both free bases and salts) and the corresponding *N*,*O*-diacetyl derivatives **27** and **28**, excluding the data reported in the anomalous syntheses highlighted above,[13b,15a] is given below (Table 1). It is known that hydrogen-bonding systems do not always give consistent measurements for specific rotation,[40] and as such judgements based upon specific rotation alone should be regarded with caution. In this system, specific rotation is not diagnostic of relative stereochemistry due to the reported similarities between the specific rotations for jaspine B **5**, 2-epi-jaspine B **6** and their derivatives. There is seemingly only one major inconsistency within this set of data $\{[\alpha]_D^{24} = +76.0$ (*c* 0.2, $CHCl_3$) reported by Kim et al.[12b] for the free base of jaspine B **5**} otherwise the values for jaspine B **5**, 2-*epi*-jaspine B **6** and the TFA salts of both diastereoisomers are typically in the range +10 to +20, and upon conversion to the corresponding *N*,*O*-diacetyl derivatives, lie approximately within the range −15 to −30 (Table 1).

5.2. ^{1}H and ^{13}C NMR spectroscopic data

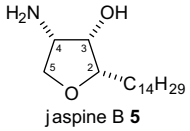
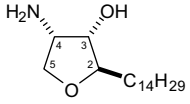
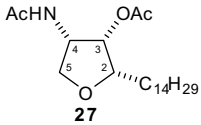
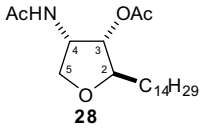
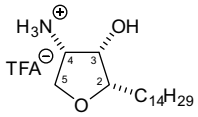
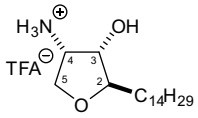
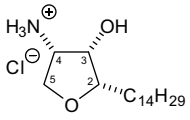
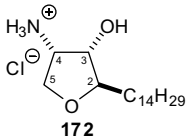
A thorough inspection of the ^{1}H and ^{13}C NMR data for all reported synthetic and the naturally occurring samples of

Table 1. Specific rotation data for jaspine B **5**, 2-*epi*-jaspine B **6**, and the corresponding *N*,*O*-diacetyl derivatives **27** and **28**, TFA salts **61** and **62**, and HCl salts **75** and **172**

Compound	Source	Specific rotation
 jaspine B **5**	Higa (Ref. 5)	$[\alpha]_D = +18.0$ (c 0.1, EtOH)
	Shaw (Ref. 14)	$[\alpha]_D^{28} = +13.3$ (c 0.03, EtOH)
	Srinivasan (Ref. 20b)	$[\alpha]_D^{25} = +17.7$ (c 0.4, EtOH)
	Prasad (Ref. 18)	$[\alpha]_D = +17.5$ (c 0.4, EtOH)
	Davies (Refs. 19a,19c)	$[\alpha]_D^{23} = +17.5$ (c 0.3, EtOH)
	Overkleeft (Ref. 12a)	$[\alpha]_D^{22} = +4.8$ (c 1.0, MeOH)
	Shaw (Ref. 14)	$[\alpha]_D^{28} = +8.5$ (c 0.047, MeOH)
	Kim (Ref.12b)	$[\alpha]_D^{23} = +19.7$ (c 0.5, MeOH)
	Davies[d]	$[\alpha]_D^{18} = +9.4$ (c 0.3, MeOH)
	Marco (Ref. 17)	$[\alpha]_D^{25} = +9.0$ (c 1.5, $CHCl_3$)
	Debitus (Ref. 11)	$[\alpha]_D^{20} = +7.0$ (c 0.1, $CHCl_3$)
	Kim (Ref. 12b)[a]	$[\alpha]_D^{24} = +76.0$ (c 0.2, $CHCl_3$)
	Davies[d]	$[\alpha]_D^{18} = +6.5$ (c 0.47, $CHCl_3$)
 2-*epi*-jaspine B **6**	Kim (Ref. 9)	$[\alpha]_D^{23} = +14.8$ (c 0.002, EtOH)
	Davies[d]	$[\alpha]_D^{18} = +12.7$ (c 0.65, EtOH)
	Kim (Ref. 12b)	$[\alpha]_D^{23} = +23.2$ (c 1.0, MeOH)
	Overkleeft (Ref. 12a)	$[\alpha]_D^{22} = +15.0$ (c 1.0, MeOH)
	Davies (Ref. 19c)	$[\alpha]_D^{21} = +16.4$ (c 0.85, MeOH)
	Datta (Ref. 13b)[c]	$[\alpha]_D^{25} = +9.6$ (c 0.11, $CHCl_3$)
	Davies[d]	$[\alpha]_D^{18} = +11.8$ (c 0.65, $CHCl_3$)
 **27**	Kim (Ref. 12b)	$[\alpha]_D^{24} = -18.5$ (c 0.7, $CHCl_3$)
	Ramana (Ref. 16)	$[\alpha]_D^{25} = -34.6$ (c 1.0, $CHCl_3$)
	Marco (Ref. 17)	$[\alpha]_D^{25} = -28.4$ (c 1.0, $CHCl_3$)
	Overkleeft (Ref. 12a)	$[\alpha]_D^{22} = -22.6$ (c 1.0, $CHCl_3$)
	Davies (Ref. 19c)	$[\alpha]_D^{23} = -26.4$ (c 0.5, $CHCl_3$)
	Ramana (*ent.*, Ref. 16)	$[\alpha]_D^{25} = +29.0$ (c 1.0, $CHCl_3$)
	Rao (Ref. 13a)[b]	$[\alpha]_D^{25} = -28.8$ (c 1.1, $CHCl_3$)
 **28**	Overkleeft (Ref. 12a)	$[\alpha]_D^{22} = -15.4$ (c 1.0, $CHCl_3$)
	Davies (Ref. 19c)	$[\alpha]_D^{22} = -14.6$ (c 0.5, $CHCl_3$)
 **61**	Rao (Ref. 13a)	$[\alpha]_D^{25} = +17.1$ (c 0.4, EtOH)
	Du (Ref. 15b)	$[\alpha]_D^{25} = +11.0$ (c 1.0, $CHCl_3$)
 **62**	Rao (Ref. 13a)	$[\alpha]_D^{25} = +14.5$ (c 1.5, EtOH)
 **75**	Davies (Ref. 19c)	$[\alpha]_D^{23} = +2.6$ (c 0.4, MeOH)
 **172**	Davies (Ref. 19c)	$[\alpha]_D^{21} = +15.5$ (c 0.9, MeOH)

[a] A personal communication from the corresponding author has confirmed the value for this specific rotation.
[b] Data kindly supplied in a personal communication from the corresponding author.
[c] Stereochemistry re-assigned in this review (see Section 4.4).
[d] Value obtained for this review.

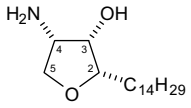
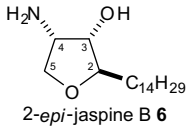
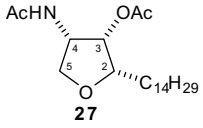
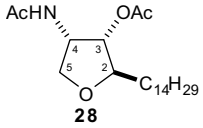
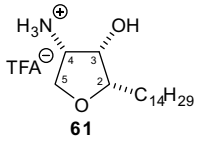
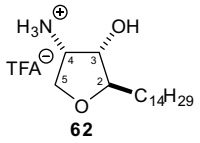
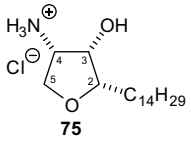
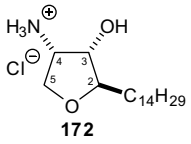
Table 2. Comparison of reported ^{1}H NMR data for jaspine B **5**, 2-*epi*-jaspine B **6**, and the corresponding *N*,*O*-diacetyl derivatives **27** and **28**, TFA salts **61** and **62**, and HCl salts **75** and **172**

Compound	Entry	Source	Solvent	C(2)*H*	C(3)*H*	C(4)*H*	C(5)H_A	C(5)H_B
 jaspine B **5**	1	Higa (Ref. 5)	MeOD	3.81 dt	3.86 dd	3.51 dt	3.43 dd	3.90 dd
	2	Shaw (Ref. 14)[a]	MeOD	3.73–3.78 m	3.92 qt	3.49–3.69 m	3.49–3.69 m	4.01–4.03 m
	3	Srinivasan (Ref. 20b)[a]	MeOD	3.69–3.75 m	3.84–3.88 m	3.63–3.67 m	3.49–3.53 m	3.89–3.94 m
	4	Debitus (Ref. 11)	$CDCl_3$	3.75 ddd	3.88 dd	3.68 dt	3.54 dd	3.95 dd
	5	Kim (Ref. 12b)[a]	$CDCl_3$	3.73 dt	3.86 dd	3.64 dt	3.50 dd	3.92 dd
	6	Marco (Ref. 17)[a]	$CDCl_3$	3.73 ddd	3.86 dd	3.65 m	3.51 dd	3.92 dd
	7	Overkleeft (Ref. 12a)	$CDCl_3$	3.75 ddd	3.87 dd	3.59 br m	3.53 dd	3.92 dd
	8	Prasad (Ref. 18)[a,b]	$CDCl_3$	3.71–3.76 m	3.86–3.88 m	6.62–3.70 m	3.50–3.53 m	3.91–3.95 m
	9	Davies (Refs. 19a,19c)	$CDCl_3$	3.74 td	3.87 t	3.61–3.69 m	3.50 dd	3.91 t
	10	Koskinen (Ref. 13c)[a,c]	$CDCl_3$	3.73 ddd	3.87 dd	3.64 m	3.51 dd	3.92 dd
 2-*epi*-jaspine B **6**	11	Datta (Ref. 13b)[a,d]	$CDCl_3$	Not reported	3.63 m	3.40–3.48 m	3.40–3.48 m	4.14 dd
	12	Kim (Ref. 12b)[a]	$CDCl_3$	3.60 dd	3.62 m	3.45 m	3.39 dd	4.11 dd
	13	Kim (Ref. 9)[a]	$CDCl_3$	3.58–3.62 m	3.58–3.62 m	3.45 q	3.36 ABq	4.20 ABq
	14	Davies (Refs. 19a,19c)	$CDCl_3$	3.60–3.64 m	3.60–3.64 m	3.46–3.49 m	3.37–3.47 m	4.11–4.15 m
	15	Overkleeft (Ref. 12a)	$CDCl_3$/MeOD	3.74 m	4.04 t	3.67 quin	3.75 dd	4.13 dd
 **27**	16	Higa (Ref. 5)	$CDCl_3$	3.90 ddd	5.38 dd	4.81 dq	3.60 dd	4.15 dd
	17	Debitus (Ref. 11)	$CDCl_3$	3.93 ddd	5.42 dd	4.85 dq	3.62 dd	4.11 dd
	18	Kim (Ref. 12b)[a]	$CDCl_3$	3.90 m	5.38 dd	4.81 dddd	3.59 t	4.07 t
	19	Ramana (Ref. 16)[a]	$CDCl_3$	3.85–3.93 m	5.37 dd	4.80 dq	3.58 dd	4.06 dd
	20	Marco (Ref. 17)[a]	$CDCl_3$	3.90 ddd	5.40 dd	4.83 qd	3.60 t	4.09 t
	21	Overkleeft (Ref. 12a)	$CDCl_3$	3.90 m	5.38 dd	4.81 ddd	3.59 dd	4.07 dd
	22	Yakura (Ref. 20a)[a]	$CDCl_3$	3.86–.395 m	5.38 dd	4.82 qd	3.60 t	4.08 t
	23	Davies (Refs. 19a,19c)	$CDCl_3$	3.91 ddd	5.38 dd	4.82 ddd	3.60 t	4.10 t
	24	Rao (Ref. 13a)[a,e]	$CDCl_3$	3.80–3.90 m	5.30–5.40 m	4.70–4.80 m	3.50–3.60 m	4.00–4.10 m
 **28**	25	Overkleeft (Ref. 12a)	$CDCl_3$	3.86 m	4.91 dd	4.65 m	3.52 dd	4.17 dd
	26	Davies (Refs. 19a,19c)	$CDCl_3$	3.90–3.93 m	4.95–4.97 m	4.67–4.73 m	3.55–3.58 m	4.21–4.24 m
 **61**	27	Higa (Ref. 5)	MeOD	3.79 dd	4.25 dd	3.91 dd	3.71 dt	3.88 m
	28	Du (Ref. 15b)[a]	MeOD	3.79 dd	4.23 dd	3.82–3.93 m	3.70 dt	3.82–3.93 m
		Rao (Ref. 13a)[a,e]	MeOD	3.75–3.80 m	4.20–4.25 m	3.80–3.90 m	3.65–3.75 m	3.80–3.90 m
 **62**	29	Rao (Ref. 13a)[a]	MeOD	3.64–3.75 m	4.10–4.17 m	3.64–3.75 m	3.64–3.75 m	3.98–4.04 m
 **75**	30	Davies (Ref. 19c)	MeOD	3.73 ddd	4.28 dd	3.88–3.96 m	3.83 q	3.88–3.96 m
 **172**	31	Davies (Ref. 19c)	MeOD	3.70–3.77 m	4.04–4.06 m	3.70–3.77 m	3.70–3.77 m	4.16–4.19 m

[a] Protons assigned in this review.
[b] Resonance at 3.62–3.70 ppm confirmed in a personal communication from the corresponding author.
[c] Data kindly supplied in a personal communication from the corresponding author.
[d] Stereochemistry re-assigned in this review (see Section 4.4).
[e] Spectra kindly supplied in a personal communication from the corresponding author (peaks quoted ± 0.05 ppm).

jaspine B **5** and comparison with that of 2-*epi*-jaspine B **6** reveals that Datta's proposed data for the natural product (Tables 2 and 3, entry 11) in fact bears close resemblance to that of the 2-*epi*-jaspine B **6** (Tables 2 and 3, entries 12–14) and displays a characteristic peak at 4.14 ppm in the ^{1}H NMR spectrum corresponding to one of the C(5) protons; the all-*cis* stereochemistry of 2-alkyl-3-hydroxy-4-amino-tetrahydrofuran derivatives is characterised by the absence

Table 3. Comparison of reported ^{13}C NMR data for jaspine B **5**, 2-*epi*-jaspine B **6**, and the corresponding *N*,*O*-diacetyl derivatives **27** and **28**, TFA salts **61** and **62**, and HCl salts **75** and **172**

Compound	Entry	Source	Solvent	C(2)	C(3)	C(4)	C(5)
 jaspine B **5**	1	Higa (Ref. 5)	MeOD	84.3	73.3	56.0	72.1
	2	Shaw (Ref. 14)[a]	MeOD	83.5	71.3	54.4	70.5
	3	Srinivasan (Ref. 20b)[a]	MeOD	83.2	72.3	54.4	71.8
	4	Debitus (Ref. 11)	$CDCl_3$	83.1	72.2	54.2	71.6
	5	Kim (Ref. 12b)[a]	$CDCl_3$	83.2	72.3	54.3	71.8
	6	Marco (Ref. 17)[a]	$CDCl_3$	83.3	72.4	54.4	71.8
	7	Overkleeft (Ref. 12a)	$CDCl_3$	82.9	71.8	54.3	71.7
	8	Prasad (Ref. 18)[a]	$CDCl_3$	84.3	70.9	54.4	68.9
	9	Davies (Refs. 19a,19c)	$CDCl_3$	83.1	72.4	54.4	71.8
	10	Koskinen (Ref. 13c)[a,b]	$CDCl_3$	83.2	72.3	54.3	71.7
 2-*epi*-jaspine B **6**	11	Datta (Ref. 13b)[a,c]	$CDCl_3$	85.1	74.6	52.5	73.1
	12	Kim (Ref. 12b)[a]	$CDCl_3$	85.2	74.8	52.7	73.1
	13	Kim (Ref. 9)[a]	$CDCl_3$	85.2	74.7	52.6	73.1
	14	Davies (Refs. 19a,19c)	$CDCl_3$	85.3	74.8	52.6	73.2
	15	Overkleeft (Ref. 12a)	$CDCl_3$/MeOD	84.4	73.1	52.0	68.0
 **27**	16	Kim (Ref. 12b)[a]	$CDCl_3$	81.2	73.5	51.3	69.9
	17	Ramana (Ref. 16)[a]	$CDCl_3$	81.2	73.5	51.3	69.9
	18	Marco (Ref. 17)[a]	$CDCl_3$	81.2	73.6	51.4	70.0
	19	Overkleeft (Ref. 12a)[a]	$CDCl_3$	81.1	71.4	51.2	69.7
	20	Yakura (Ref. 20a)[a]	$CDCl_3$	81.2	73.6	51.3	70.0
	21	Davies (Refs. 19a,19c)	$CDCl_3$	81.2	73.5	51.3	69.8
	22	Rao (Ref. 13a)[a,d]	$CDCl_3$	81.0	73.5	51.5	70.0
 **28**	23	Overkleeft (Ref. 12a)[a]	$CDCl_3$	84.0	76.6	49.8	69.7
	24	Davies (Refs. 19a,19c)	$CDCl_3$	84.2	77.1	49.9	69.9
 **61**	25	Higa (Ref. 5)[a]	MeOD	84.3	70.9	54.3	68.9
	26	Du (Ref. 15b)[a]	MeOD	84.4	70.9	54.3	68.9
		Rao (Ref. 13a)[a,d]	MeOD	85.0	71.5	55.0	69.5
 **62**	27	Rao (Ref. 13a)[a]	MeOD	85.2	74.3	53.7	69.4
 **75**	28	Davies (Ref. 19c)	MeOD	83.4	69.9	53.4	68.0
 **172**	29	Davies (Ref. 19c)	MeOD	83.8	73.0	52.3	68.0

[a] Carbons assigned in this review.
[b] Data kindly supplied in a personal communication from the corresponding author.
[c] Stereochemistry re-assigned in this review (see Section 4.4).
[d] Spectra kindly supplied in a personal communication from the corresponding author (peaks quoted ± 0.5 ppm).

of peaks above 4 ppm in the ^{1}H NMR spectra in $CDCl_3$, as found for jaspine B **5** (Table 2, entries 4–10).

6. Conclusion

Since the isolation of jaspine B (pachastrissamine) was first communicated (2002), there have been 13 independent syntheses of this natural product. This review has highlighted some inconsistencies between the data reported for some synthetic samples of jaspine B and that of the naturally occurring compound. However, the majority of syntheses (including those of 2-*epi*-jaspine B) corroborate the original structural assignment. The wealth of data summarised in this review serves to confirm the structure and (2*S*,3*S*,4*S*)-absolute configuration of this natural product, which was correctly assigned by Higa et al. in the first instance and then independently by Debitus and co-workers.

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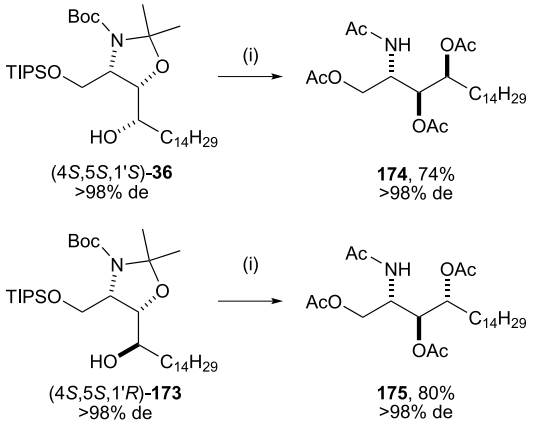

Scheme 21. Reagents and conditions: (i) HCl (3 M, aq), MeOH, 50 °C, 3 h, then Ac_2O, DMAP, pyridine, rt, 12 h.

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