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Rapid access to jaspine B and its enantiomer

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ABSTRACT

A rapid access to jaspine B and its enantiomer *ent*-jaspine B from a 2,3-aziridino-γ-lactone is reported. This synthesis relies on a one pot regioselective aziridine ring-opening followed by intramolecular cyclization to install the *cis*-amino–alcohol pattern of jaspine B and on a modified Julia olefination of the lactone followed by a diastereoselective hydrogenation for the introduction of the C14 aliphatic chain. The separation of enantiomers in the course of this synthesis was achieved by supercritical fluid chromatography. The cytotoxicity of both enantiomers was evaluated.

1. Introduction

Jaspine B (also named Pachastrissamine) (Fig. 1) is a naturally occurring anhydrophytosphingosine, which was first isolated in 2002 from the Okinawan marine sponge, *Pachastrissa* sp.[1] One year later Debitus et al.[2] also extracted this natural D-*ribo*-phytosphingosine derivative from the sponge *Jaspis* sp. collected in Vanuatu. This natural jaspine B was reported to exhibit submicromolar cytotoxicity against various cell lines.[1,2] We found in particular that jaspine B displays a strong dose- and time-dependent cytotoxicity towards melanoma cells (murine B16 and human SK-Me128).[3] However, despite a significant interest in the molecular mechanism of cell death induced by jaspine B,[3,4] this likely complex and multi-target mode of action has not been characterized fully. Recently, Kim et al. also highlight the potential use of jaspine B as a therapeutic agent against hyperproliferative diseases, such as melanoma.[5]

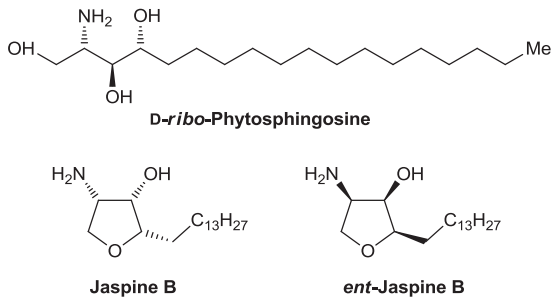

Fig. 1. Structure of D-*ribo*-phytosphingosine, jaspine B and its enantiomer.

Due to this remarkable biological activity and its relatively simple structural features, jaspine B has stimulated considerable interest of the synthetic community.[6,7] To go deeper in the understanding of the structure–activity relationships of this natural compound, many analogues were synthesized[8] as well as diastereoisomers of jaspine B.[4a,b,6a,7f–j,8a,9] The enantiomer *ent*-jaspine B was not the deal of such an effort from the synthetic point of view[4b,7k,9a,10] and study of its biological activity remains limited.[4b,9a]

In this paper, we wish to report a rapid synthetic access to jaspine B and its enantiomer and the evaluation of their cytotoxic activity.

2. Results and discussion

2.1. Synthetic approach

Recently, we described the synthesis of phytosphingosine and jaspine B analogues containing an aziridine ring.[8e] These syntheses were based on an aziridino-γ-lactone as a common precursor

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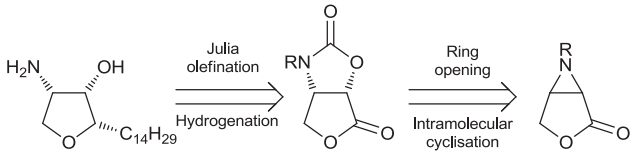
(Scheme 1). We envisioned that this versatile intermediate was ideally suited to assemble the jaspine B all-*cis* tetrahydrofuran framework according to the following retrosynthetic scheme (Scheme 1).



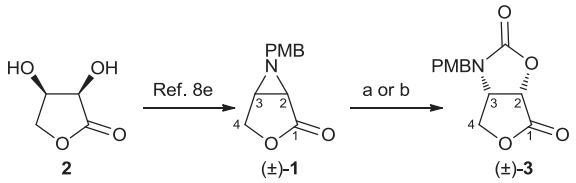
Scheme 1. Retrosynthetic approach to jaspine B.

The two main features of this approach are: (1) the construction of the *cis*-amino–alcohol pattern through a one pot regioselective aziridine ring-opening followed by intramolecular cyclization and (2) the introduction of the C14 aliphatic chain through a modified Julia olefination of the lactone followed by a diastereoselective hydrogenation.

2.2. Synthesis

2.2.1. Racemic route. Aziridino-γ-lactones are very useful intermediates[11] that have been used in the preparation of several amino-acids derivatives.[12]

The 2,3-aziridino-γ-lactones bearing an alkyl group on the nitrogen (Scheme 1, R=alkyl) can be regarded as non-activated aziridine-2-carboxylates. The reactivity of non-activated 2-substituted aziridines towards ring opening reaction has recently been reviewed.[13] Lee, Ha and coll. showed that the reaction of aziridines bearing an electron withdrawing group at C-2 with methyl chloroformate give oxazolidin-2-ones in a one pot process.[14] We applied this pathway to 2,3-aziridino-γ-lactone **1** (Scheme 2) so as to introduce the *cis*-amino–alcohol moiety present on the tetrahydrofuran ring of the jaspine B.

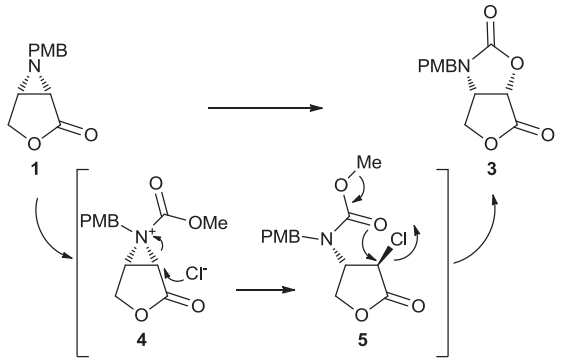


Scheme 2. Synthesis of lactone oxazolidinone **3**. Reagents and conditions: (a) $ClCO_2CH_3$, CH_3CN, reflux, 12 h, 74%; or (b) $ClCO_2CH_3$, CH_3CN, sealed tube, MW, 160 W, 100 °C, 2 h, 79%.

The racemic 2,3-aziridino-γ-lactone **1** was obtained in two steps from D-erythronolactone (**2**).[8e] Under the conditions described by Lee, Ha and coll.[14] the aziridine ring was converted to the oxazolidin-2-one **3**.

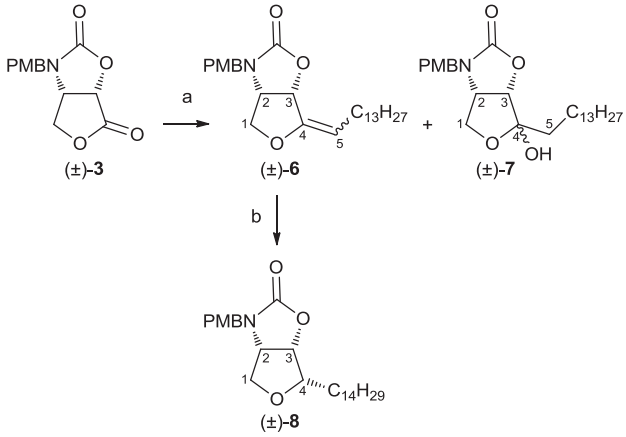
According the mechanism reported,[14] this transformation, initiated by a N-methoxycarbonylation, provides an activated aziridinium **4** that undergoes a regioselective C2–N bond cleavage by the nucleophilic chloride ion. The intramolecular cyclization of the resulting intermediate chlorocarbamate **5** gives the oxazolidin-2-one with a global retention of configuration at C-2 as a result of a double S_N2 inversion process (Scheme 3).

We were satisfied to observe that, despite the presence of the sensitive lactone,[12a] the yield was only slightly lower than those described by Lee, Ha and coll. In order to further improve the efficiency of this transformation, the reaction time was reduced by the use of microwave irradiation. Under these conditions, only 2 h were necessary to bring the reaction to completion with a 79% yield.



Scheme 3. Proposed mechanism for the oxazolidin-2-one formation.

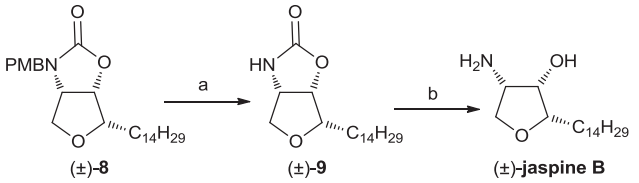
The next step en route to the jaspine B tetrahydrofuran core assembly was the introduction of the C14 alkyl chain. According to our synthetic plan, an olefination of the carbonyl function of the lactone was accomplished by a Julia modified reaction[15] using the methodology recently described by Gueyrard and coll. for the synthesis of *exo*-glycal.[16] The reaction of the lactone **3** and 2-(tetradecylsulfonyl)benzo[*d*]thiazole[17] (Scheme 4) followed by a treatment with DBU afforded the enol ether **6** as an irrelevant 2:1 mixture of *E*/*Z* isomers[18] and in a 49% yield. As appeared in the literature during the course of this work,[19] we observed that the enol ether formed was very sensitive to hydration and we could not completely avoid formation of the hemiketal **7** (23% yield after chromatography). Use of boron trifluoride etherate as described by Gueyrard, Goekjian and coll.[20] did not improve the conversion. On the other hand, purification on basic alumina instead of silica gel, allowed us to slightly increase the isolated yield in alkenes **6** to 55%.



Scheme 4. Synthesis of racemic protected jaspine B. Reagents and conditions: (a) (1) 2-(tetradecylsulfonyl)benzo[*d*]thiazole, LiHMDS, THF, −78 °C, 30 min; (2) DBU, THF, rt, 2 h, 55% in **6** and 8% in **7**; (b) H_2, $(Ph_3P)_3RhCl$, C_6H_6/EtOH, 2 h, 78%.

Hydrogenation of the olefin in compound **6** employing homogeneous catalyst $(Ph_3P)_3RhCl$[7c] furnished the fully protected racemic jaspine B (**8**) as a single diastereoisomer and in a 78% yield. The use of heterogeneous Pd/C catalyst (up to 50 mol %) did not give any hydrogenation product but only hydration product **7**.

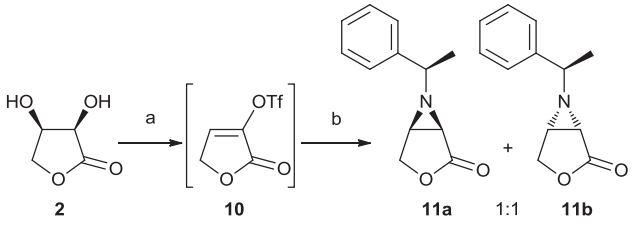
The intermediate **8**, in its enantiomeric pure form, has already been used by our group in the synthesis of jaspine B.[8d] Following the protocol described, two deprotection steps, that is oxidative elimination of the PMB-group followed by the hydrolysis of the oxazolidinone ring, allowed us to obtain the racemic jaspine B in a 60% yield (Scheme 5).



Scheme 5. Synthesis of racemic jaspine B. Reagents and conditions: (a) CAN, MeCN/H_2O, 2 h, 71%; (b) KOH, EtOH/H_2O, 85 °C, 12 h, 85%.

This six-step synthetic route validated in the racemic form, we were interested in its application to the synthesis of enantiomerically pure jaspine B and its enantiomer.

2.2.2. Chiral auxiliary route. The first option was to start the synthesis with an optically active aziridine. In this aim, we reproduced the two-step synthesis of 2,3-aziridino-γ-lactone starting from D-erythronolactone (2) via the triflate derivative **10** with the (*R*)-(+)-α-methylbenzylamine. A mixture of two diastereoisomeric aziridino-γ-lactone **11a** and **11b** was obtained in a 21% yield over the two steps (Scheme 6).



Scheme 6. Synthesis of optically active 2,3-aziridino-γ-lactones. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, −78 °C to −30 °C, 3.5 h; (b) (*R*)-(+)-α-methylbenzylamine, DMF, −30 °C, 12 h, 21% over two steps.

Due to the lower reactivity of α-methylbenzylamine compared to methoxy-substituted benzylamines in the tandem Michael-type addition/cyclization leading to the aziridine,[12a] the reaction time at −30 °C necessary for the completion was much longer and the competitive opening of the lactone ring by the amine may explain the somewhat moderate yield.[12b] This aziridination reaction was also conducted with enantiomerically pure (*R*)-*p*-methoxy-α-methylbenzylamine. The use of this chiral auxiliary did not improve the yield of the reaction. The two (*R*)-*p*-methoxy-α-methylbenzyl substituted aziridines were isolated and characterized including by X-ray diffraction crystallography (see Supplementary data).

Even after several thorough chromatographies on silica gel only milligramme-scale samples of each diastereoisomer **11a** and **11b** could be isolated. Nevertheless, X-ray crystallography analysis of compound **11a** allowed its unambiguous structural assignment (Fig. 2).

The mixture of diastereoisomers **11** was treated with methyl chloroformate in acetonitrile under MW irradiation to give the two diastereoisomeric oxazolidinones **12a** and **12b** that were separated by chromatography on silica gel (Scheme 7). The yield (25% for each diastereoisomer) was lower than in the *p*-methoxybenzyl racemic series.

This moderate yield with α-methylbenzyl substituted aziridine may deserve comments. Indeed, Lee, Ha and coll. described transformation of *N*-[(*R*)-(+)-α-methylbenzyl]aziridines-2-carboxylates to 5-functionalized oxazolidin-2-ones in almost quantitative yield.[14] Thus, the presence of the α-methylbenzyl group instead of the *p*-methoxybenzyl does not by itself explain the lowering of the yield. Nevertheless, this trend could be expected since it has already be shown that *N*-benzyl-2,3-aziridino-γ-lactones have a much lower reactivity towards nucleophilic aziridine ring opening than the *N*-benzyl-2-acyl-aziridines.[12a] This lack of reactivity was thus not only attributed to the poor electron-withdrawing character of the benzyl group but also to the competitive electrophilic behaviour of the lactone ring.

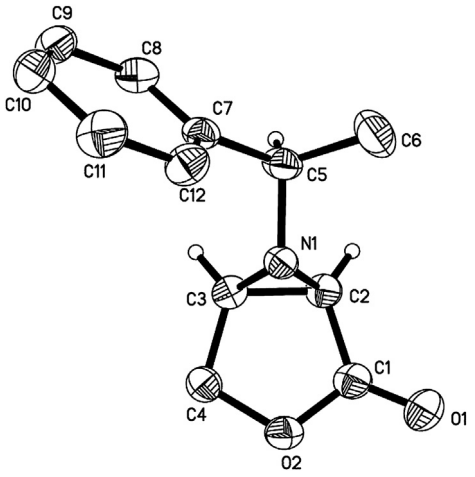
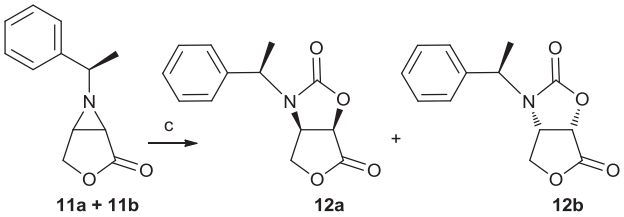


Fig. 2. Molecular view of the aziridino-γ-lactone **11a** in the solid state (thermal ellipsoids at 50% probability); hydrogen atoms are omitted for clarity excepted on asymmetric carbons.



Scheme 7. Synthesis of optically active lactone oxazolidinones. Reagents and conditions: (a) $ClCO_2CH_3$, CH_3CN, sealed tube, MW, 160 W, 100 °C, 2.5 h, 50%.

The two diastereoisomers **12a** and **12b** were crystallized and X-ray analysis allowed their structural assignment (Figs. 3 and 4).

The yield obtained in the two first steps of this synthesis using (*R*)-(+)-α-methylbenzylamine as chiral auxiliary, much lower than in the *p*-methoxybenzyl racemic series, associated with fastidious chromatographies required for the separation of the diastereoisomers led us to consider another option for the synthesis of enantiomerically pure jaspine B and its enantiomer. We developed a separation method of both enantiomers of the racemic protected jaspine B **8**.

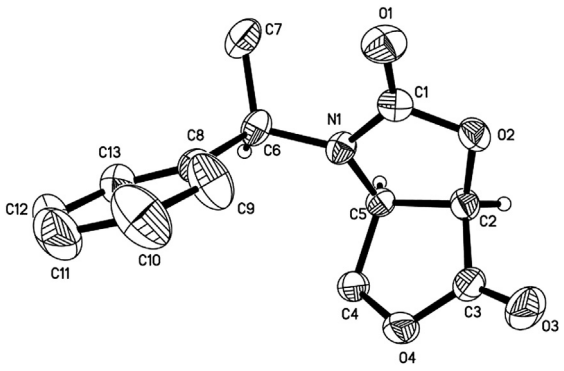


Fig. 3. Molecular view of compound **12a** in the solid state (thermal ellipsoids at 50% probability); hydrogen are omitted for clarity excepted on asymmetric carbons.

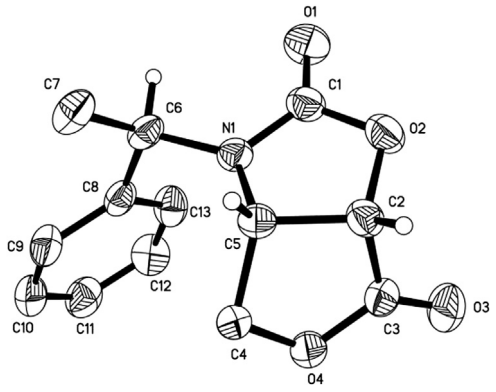


Fig. 4. Molecular view of compound **12b** in the solid state (thermal ellipsoids at 50% probability); hydrogen atoms are omitted for clarity excepted on asymmetric carbons.

2.2.3. Enantiomers separation. The resolution of enantiomers by supercritical fluid chromatography (SFC) is a flourishing technology. The environmental and practical benefits of SFC (e.g., less solvent used, higher resolution, shorter separation times,…) are already well-known.[21] It is even sometimes considered that it is more 'time efficient' to synthesize racemic mixtures and then chromatographically separate the enantiomers than to develop asymmetric syntheses of the drug candidates of interest.[22] An overview of SFC applications for chiral separations covering the literature from 2000 has recently been published.[23]

In our case, the best resolution was achieved by semi-preparative SFC on a Chiralpak IC column (5 μm silica particles immobilized with cellulose tris-(3,5-dichlorophenylcarbamate)) with 25% of a CH_2Cl_2/MeOH mixture (80:20, v/v) as an additive in a CO_2 mobile phase (Fig. 5). This separation could be run on more than 100 mg and both enantiomers were obtained in high efficiency and purity (80% global yield).

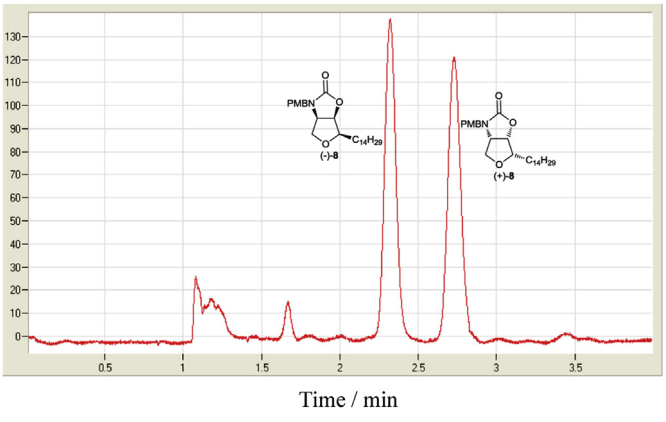


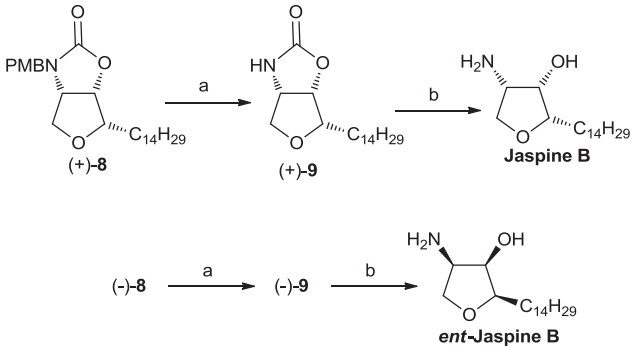
Fig. 5. Separation of the enantiomers of (±)-**8** by SFC.

Each enantiomer of protected jaspine B ((+)-**8** and (−)-**8**) was submitted to the same two steps deprotection protocol leading to jaspine B and its enantiomer *ent*-jaspine B in 60% yield (Scheme 8).

Enantiomerically pure jaspine B and its enantiomer were thus synthetized in six steps from commercially available D-erythronolactone in 7% overall yield.

2.3. Biological evaluation

Despite the synthetic efforts dedicated to the synthesis of various diastereoisomers of jaspine B, only two groups reported



Scheme 8. Synthesis of jaspine B and *ent*-jaspine B. Reagents and conditions: (a) CAN, $MeCN/H_2O$, 2 h; (b) KOH, $EtOH/H_2O$, 85 °C, 12 h, 60% over two steps.

biological evaluation of *ent*-jaspine B: Rao and coll. evaluated its cytotoxicity[9a] while Fujii, Oishi and coll. assessed its inhibitory potency against sphingosine kinases.[4b] In these two studies, the results obtained with *ent*-jaspine B proved to be very close to that of the natural enantiomer. On the other hand, Casas and Delgado and coll.[4a] showed that inversion of C-2 and/or C-3 stereocenters provides significantly less toxic compounds.

In order to go further in the understanding of the influence of the absolute configuration on the cytotoxic activity, the cytotoxicity of jaspine B and *ent*-jaspine B was examined on GM637 (normal fibroblast), HTC116 (human colon carcinoma) and U2OS (human osteosarcoma) cells. The IC_{50} of the compounds are reported in Table 1.

Table 1
Cytotoxicity of jaspine B and *ent*-jaspine B

Compound	IC_{50} (μM)		
	GM637	HTC116	U2OS
Jaspine B	0.4	0.7	0.17
ent-Jaspine B	6	5	4

In all cell lines, the natural compound, with IC_{50} values in submicromolar range, proved to be significantly more cytotoxic than its enantiomer. These results indicate that the absolute configuration of the tetrahydrofuran jaspine B is indeed determinant for the biological activity of this natural compound. Nevertheless, it is noteworthy that the cytotoxicities obtained for the unnatural compound are in the micromolar range. These values thus justify the study of the enantiomer of jaspine B itself for further target identification and structural optimization.

3. Conclusions

In summary, we have developed a rapid synthesis of jaspine B and *ent*-jaspine B involving six synthetic steps from commercially available D-erythronic γ-lactone and a chiral separation by supercritical fluid chromatography (SFC). This synthesis illustrated well the versatility of 2,3-aziridino-γ-lactone intermediates, alternatively taking advantage of its different reactivities: first, that of the aziridine ring to install the *cis*-amino–alcohol moiety through a one pot regioselective ring-opening followed by intramolecular cyclization and, second, the reactivity of the lactone to introduce the aliphatic chain by a Julia modified olefination followed by a diastereoselective hydrogenation. Thanks to an efficient enantiomeric resolution by a chiral SFC, this route was easily amenable to the preparation of natural jaspine B and its enantiomer. Biological evaluation of the synthesized compounds confirmed the influence of the absolute configuration of the natural product on its

cytotoxicity. Yet the cytotoxicity retained by the *ent*-jaspine B (in the micromolar range) justifies the interest of a synthetic access to both enantiomers.

4. Experimental part

4.1. General methods

The following solvents and reagents were dried prior to use: CH_2Cl_2, MeOH (from calcium hydride), Et_2O, petroleum ether, THF (freshly distilled from sodium/benzophenone). Analytical thin layer chromatography (TLC) was performed using Merck silica gel $60F_{254}$ precoated plates. Chromatograms were observed under UV light and/or were visualized by heating plates that were dipped in 10% phosphomolybdic acid in ethanol. Column chromatographies were carried out with SDS 35–70 μm flash silica gel. NMR spectroscopic data were obtained with Bruker Advance 300. Chemical shifts are quoted in parts per million (ppm) relative to residual solvent peak. *J* values are given in hertz. Assignments of chemical shifts are described according to the numbering drawn on Scheme 2 for lactones and on Scheme 4 for all other compounds. Mass spectrometry (MS) data were obtained on a ThermoQuest TSQ 7000 spectrometer, high-resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL. Optical rotations were measured on a Jasco P-2000 polarimeter. $[\alpha]_D$ values are given in deg dm^{-1} cm^3 g^{-1}.

For crystallographic analysis, the selected crystals were mounted on a glass fibre using perfluoropolyether oil and cooled rapidly in a stream of cold N_2. Crystallographic data of the structures for compounds **11a**, **12a** and **12b** were collected on a Bruker-AXS Quazar APEX II diffractometer using a 30 W air-cooled microfocus source (ImS) with focussing multilayer optics at a temperature of 193(2) K, with Mo Kα radiation (wavelength=0.71073 Å) by using phi- and omega-scans. The data were integrated with SAINT, and an empirical absorption correction with SADABS was applied.[24] The structures were solved by direct methods, using SHELXS-97,[25] and refined using the least-squares method on F^2.[25] All non-H atoms were treated anisotropically. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-935731 (**11a**), CCDC-935732 (**12a**) and CCDC-935733 (**12b**). These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or deposit@ccdc.cam.ac.uk).

4.2. Synthesis

4.2.1. (3aS,6aS*)-3-(4-Methoxybenzyl)dihydrofuro[3,4-d]oxazole-2,6(3H,6aH)-dione (**3**). Method A*: To a solution of **1** (285 mg, 1.30 mmol) in CH_3CN (5 mL) was added methyl chloroformate (151 μL, 1.95 mmol) and the mixture was refluxed for 12 h. After cooling to rt, the mixture concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (EtOAc/CH_2Cl_2 1:9) to give the oxazolidinone **3** (253 mg, 74%) as a white amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.25–7.15 (m, 2H, H_{ar}); 7.00–6.90 (m, 2H, H_{ar}); 4.95 (d, 1H, 2-H, $J_{2\text{-}3}$=7.9); 4.67 (d, 1H, CH_2N, *J*=15.0); 4.35 (ddd, 1H, 3-H, $J_{3\text{-}2}$=7.9, $J_{3\text{-}4a}$=4.1, $J_{3\text{-}4b}$=1.5); 4.30 (AB of an ABX, 2H, 4a-H and 4b-H, $J_{4a\text{-}4b}$=10.8, $J_{4a\text{-}3}$=4.1, $J_{4b\text{-}3}$=1.5); 4.29 (d, 1H, CH_2N, *J*=14.9); 3.81 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.4 (C-1); 159.9 (*C*–OMe); 155.9 (C=O); 129.8 (C_{ar}); 126.0 (Cq_{ar}); 114.7 (C_{ar}); 69.8 (C-2); 68.5 (C-4); 55.4 (C-3); 55.2 (OMe); 46.8 (CH_2N). HRMS *m*/*z*: calcd for $C_{13}H_{14}NO_5$ $[M+H]^+$: 264.0872; found: 264.0863.

Method B: To a solution of **1** (472 mg, 2.16 mmol) in CH_3CN (7 mL) in a 10 mL glass pressure vial equipped with a stir bar was added methyl chloroformate (250 μL, 3.23 mmol). The pressure vial was closed using a PTFE-silicon septum (vial and septum available from CEM Corporation). Then the reaction mixture was submitted in a sealed tube to microwave irradiation (CEM Discover™ reactor, 160 W, 100 °C) for 2 h. After cooling, the reaction mixture was concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (EtOAc/CH_2Cl_2 1:9) to give the oxazolidinone **3** (451 mg, 79%) as a white amorphous solid.

4.2.2. (3aS,6aS*,E)-3-(4-Methoxybenzyl)-6-tetradecylidenetetrahydrofuro[3,4-d]oxazol-2(3H)-one (E-**6**) and (3aS*,6aS*,Z)-3-(4-methoxybenzyl)-6-tetradecylidenetetrahydrofuro[3,4-d]oxazol-2(3H)-one (Z-**6**).* To a solution of lactone **3** (75 mg, 0.29 mmol) and 2-(tetradecylsulfonyl)benzo[*d*]thiazole (135 mg, 0.34 mmol) in anhydrous THF (2 mL) under nitrogen at −78 °C was added dropwise a solution of LiHMDS (1.0 M in THF, 570 μL, 0.57 mmol) over 10 min. The reaction mixture was stirred at that temperature for 30 min and quenched by addition of water. After hydrolysis, the mixture was extracted with EtOAc (3×10 mL). The combined organic extracts were dried over magnesium sulfate and concentrated to dryness. The residue was dissolved in anhydrous THF (6 mL) and DBU (98 μL, 0.57 mmol) was added. After 2 h stirring, the reaction mixture was concentrated to dryness and the resulting residue was purified by flash chromatography on basic alumina (EtOAc/CH_2Cl_2/petroleum ether 6:24:70) to give the compound **6** (70 mg, 55%) as a 2:1 mixture of *E* and *Z* isomers. An aliquot of this mixture was purified by preparative TLC (EtOAc/CH_2Cl_2/petroleum ether 4:1:5) to characterize the two isomers.

(*E*)-**6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.25–7.15 (m, 2H, H_{ar}); 6.95–6.85 (m, 2H, H_{ar}); 5.32 (dd, 1H, 3-H, $J_{3\text{-}2}$=7.9, $J_{3\text{-}5}$=1.1); 5.13 (td, 1H, 5-H, $J_{5\text{-}6}$=8.1, $J_{5\text{-}3}$=1.1); 4.67 (d, 1H, CH_2N, *J*=15.0); 4.18 (d, 1H, CH_2N, *J*=14.9); 4.16 (ddd, 1H, 2-H, $J_{2\text{-}3}$=7.9, $J_{2\text{-}1a}$=4.4, $J_{2\text{-}1b}$=1.4); 4.01 (dd, 1H, 1b-H, $J_{1b\text{-}1a}$=10.2, $J_{1b\text{-}2}$=1.5); 3.80 (s, 3H, OMe); 3.71 (dd, 1H, 1a-H, $J_{1b\text{-}1a}$=10.2, $J_{1a\text{-}2}$=4.7); 2.20–1.90 (m, 2H, 6-H); 1.40–1.15 (m, 22H, 7-H to 17-H), 0.98–0.84 (3H, m, 18-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.6 (*C*–OMe); 157.2 (C=O); 152.0 (C-4); 129.6 (C_{ar}); 127.1 (Cq_{ar}); 114.4 (C_{ar}); 106.8 (C-5); 73.2 (C-3); 70.6 (C-1); 58.2 (C-2); 55.3 (OMe); 46.6 (CH_2N); 32.0, 30.2, 29.7 (4C), 29.6, 29.5, 29.4, 29.2, 26.7, 22.7 (C-6 to C-17); 14.2 (C-18). MS (CI/NH_3): *m*/*z*=461 ($[M+NH_4]^+$). HRMS *m*/*z*: calcd for $C_{27}H_{42}NO_4$ $[M+H]^+$: 444.3114; found: 444.3125.

(*Z*)-**6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.25–7.15 (m, 2H, H_{ar}); 6.95–6.85 (m, 2H, H_{ar}); 5.12 (d, 1H, 3-H, $J_{3\text{-}2}$=7.9); 4.80 (t, 1H, 5-H, $J_{5\text{-}6}$=7.4); 4.68 (d, 1H, CH_2N, *J*=15.0); 4.16 (d, 1H, CH_2N, *J*=14.9); 4.14 (ddd, 1H, 2-H, $J_{2\text{-}3}$=7.7, $J_{2\text{-}1a}$=4.9, $J_{2\text{-}1b}$=1.6); 4.08 (dd, 1H, 1b-H, $J_{1b\text{-}1a}$=10.2, $J_{1b\text{-}2}$=1.6); 3.81 (s, 3H, OMe); 3.80 (dd, 1H, 1a-H, $J_{1b\text{-}1a}$=10.1, $J_{1a\text{-}2}$=4.8); 2.08 (q, 2H, 6-H, *J*=7.2); 1.40–1.15 (m, 22H, 7-H to 17-H), 0.98–0.84 (3H, m, 18-H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 159.6 (*C*–OMe); 157.2 (C=O); 151.7 (C-4); 129.7 (C_{ar}); 127.1 (Cq_{ar}); 114.4 (C_{ar}); 107.0 (C-5); 75.7 (C-3); 71.3 (C-1); 57.8 (C-2); 55.3 (OMe); 46.5 (CH_2N); 32.0, 29.7 (4C), 29.6, 29.5, 29.4 (2C), 29.3, 25.4, 22.7 (C-6 to C-17); 14.2 (C-18). MS (CI/NH_3): *m*/*z*=461 ($[M+NH_4]^+$). HRMS *m*/*z*: calcd for $C_{27}H_{42}NO_4$ $[M+H]^+$: 444.3114; found: 444.3136.

Compound **7** (10 mg, 8%) resulting from the hydration of the *exo*-double bond was also isolated.

7: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.25–7.15 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 4.68 (d, 1H, CH_2N, *J*=15.0); 4.59 (d, 1H, 3-H, $J_{3\text{-}2}$=7.5); 4.14 (ddd, 1H, 2-H, $J_{2\text{-}3}$=7.5, $J_{2\text{-}1a}$=3.4, $J_{2\text{-}1b}$=1.6); 4.08 (d, 1H, CH_2N, *J*=15.0); 3.90–3.80 (m, 2H, H-1); 3.79 (s, 3H, OMe); 2.70–2.20 (br s, 1H, OH); 1.96–1.82 (m, 1H, 5a-H); 1.81–1.68 (m, 1H, 5b-H); 1.55–1.40 (m, 2H, 6-H); 1.35–1.15 (m, 22H, 7-H to 17-H); 0.92–0.82 (3H, m, 18-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.6 (*C*–OMe); 157.0 (C=O); 129.6 (C_{ar}); 127.2 (Cq_{ar}); 114.4 (C_{ar}); 107.4 (C-4); 80.6 (C-3); 67.6 (C-1); 59.0 (C-2); 55.3 (OMe); 46.3 (CH_2N); 34.9 (C-5); 31.9, 29.8, 29.7 (5C), 29.6 (2C), 29.4, 23.3, 22.7 (C-6 to C-17); 14.2 (C-18). MS (CI/NH_3): *m*/*z*=479 ($[M+NH_4]^+$). HRMS *m*/*z*: calcd for $C_{27}H_{44}NO_5$ $[M+H]^+$: 462.3219; found: 462.3227.

4.2.3. (3aS,6S*,6aS*)-3-(4-Methoxybenzyl)-6-tetradecyltetrahydrofuro[3,4-d]oxazol-2(3H)-one (**8**).* A solution of compound **6** (89 mg, 0.20 mmol) (as a *Z*/*E* mixture) and $(PPh_3)_3RhCl$ (37 mg, 0.04 mmol) in benzene/EtOH (4 mL, 1:1) was stirred at 40 °C for 14 h under H_2 atmosphere. After concentration to dryness, the residue was purified by flash chromatography on silica gel (EtOAc/CH_2Cl_2/petroleum ether 6:24:70 to 10:40:50) to give the compound **8** (70 mg, 78%). All analyses were in agreement with the data reported in the literature.[8d]

4.2.4. (3aS,6S*,6aS*)-6-Ethyltetrahydrofuro[3,4-d]oxazol-2(3H)-one (**9**).* To a solution of PMB-protected compound **8** (70 mg, 0.157 mmol) in CH_3CN/H_2O (9:1) (10 mL) was added CAN (517 mg, 0.94 mmol). The mixture was stirred at rt for 12 h, then diluted with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution and with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography on silica gel (EtOAc/CH_2Cl_2 4:6) to give the compound **9** (37 mg, 72%). All analyses were in agreement with the data reported in the literature.[8d]

4.2.5. (2S,3S*,4S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (racemic jaspine B).* KOH (34.5 mg, 0.62 mmol) was added to a solution of oxazolidinone (20 mg, 0.062 mmol) in EtOH/H_2O (8:2) (1.5 mL). The mixture was heated at 85 °C for 24 h before being cooled to rt and diluted with EtOAc and brine. The mixture was extracted three times with EtOAc and the combined extracts were concentrated to dryness. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH/NH_4OH 84.2:15:0.8) to give racemic jaspine B (15.6 mg, 85%). All analyses were in agreement with the data reported in the literature.[8d]

*4.2.6. (1R,5S)-6-((R)-1-Phenylethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**11a**) and (1S,5R)-6-((R)-1-phenylethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**11b**).* To a solution of D-erythronolactone (1.55 g, 13.1 mmol) in dichloromethane (62 mL) held at −78 °C under argon were successively added pyridine (5.31 mL, 65.6 mmol) and a solution of trifluoromethanesulfonic anhydride (10.0 g, 35.4 mmol) in CH_2Cl_2 (16 mL). After 15 min of stirring at −78 °C, the reaction mixture was slowly warmed to −25 °C over a period of 3.5 h. The reaction solution was then poured into cold Et_2O (150 mL). The precipitate was filtered, and the filtrate was evaporated under reduced pressure at 0 °C. The resulting residue was rapidly purified by filtration on silica gel (Et_2O) to afford triflate **10** as a yellow oil, which was directly reacted in the next step. To a solution of compound **10** (1.68 g, 7.23 mmol) in DMF (35 mL) at −30 °C under argon was added dropwise (*R*)-(+)-α-methylbenzylamine (1.40 mL, 10.8 mmol). The reaction mixture was stirred for at −30 °C overnight before being diluted with EtOAc (50 mL) and water (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic extracts were dried over magnesium sulfate and concentrated to dryness. The resulting residue was purified by flash chromatography on silica gel (Et_2O/petroleum ether 2:1) to give (1*R*,5*S*)-6-((*R*)-1-phenylethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**11a**) (60 mg, 2%), (1*S*,5*R*)-6-((*R*)-1-phenylethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**11b**) (60 mg, 2%) and the mixture of the two diastereoisomers (460 mg, 17%).

11a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.4–7.1 (m, 5H, H_{ar}); 4.13 (d, 1H, 4a-H, $J_{4a\text{-}4b}$=9.9); 4.04 (dd, 1H, 4b-H, $J_{4b\text{-}4a}$=9.9, $J_{4b\text{-}3}$=2.9); 2.74 (dd, 1H, 3-H, $J_{3\text{-}2}$=4.4, $J_{3\text{-}4b}$=3.0); 2.67 (d, 1H, 2-H, $J_{2\text{-}3}$=4.5), 2.61 (q, 1H, CH_3CHN, *J*=6.5); 1.42 (d, 3H, CH_3CHN, *J*=6.5). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.5 (C-1); 143.0 (Cq_{ar}); 128.7 (C_{ar}); 127.7 (C_{ar}); 126.5 (C_{ar}); 69.7 (C-4); 67.1 (CH_3CH); 41.5 (C-3); 40.2 (C-2); 23.4 (CH_3CH). $[\alpha]_D^{20}$ −19.6 (*c* 0.5, $CHCl_3$). HRMS *m*/*z*: calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.1025; found: 204.1028.

11b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.4–7.2 (m, 5H, H_{ar}); 4.41 (d, 1H, 4a-H, $J_{4a\text{-}4b}$=9.9); 4.26 (dd, 1H, 4b-H, $J_{4b\text{-}4a}$=9.9, $J_{4b\text{-}3}$=3.0); 2.99 (dd, 1H, 3-H, $J_{3\text{-}2}$=4.5, $J_{3\text{-}4b}$=3.0); 2.73 (q, 1H, CH_3CHN, *J*=6.5); 2.55 (d, 1H, 2-H, $J_{2\text{-}3}$=4.5), 1.48 (d, 3H, CH_3CHN, *J*=6.5). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.2 (C-1); 142.5 (Cq_{ar}); 128.6 (C_{ar}); 127.6 (C_{ar}); 126.3 (C_{ar}); 69.4 (C-4); 66.9 (CH_3CH); 42.6 (C-3); 39.0 (C-2); 23.5 (CH_3CH). $[\alpha]_D^{20}$ −23.6 (*c* 0.4, $CHCl_3$). HRMS *m*/*z*: calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.1025; found: 204.1033.

*4.2.7. (3aR,6aR)-3-((R)-1-Phenylethyl)dihydrofuro[3,4-d]oxazole-2,6(3H,6aH)-dione (**12a**) and (3aS,6aS)-3-((R)-1-phenylethyl)dihydrofuro[3,4-d]oxazole-2,6(3H,6aH)-dione (**12b**).* The protocol used for the synthesis of **3** (method B) was applied to the mixture of aziridine lactones **11a** and **11b** (178 mg, 0.874 mmol) and methyl chloroformate (104 μL, 1.31 mmol) in CH_3CN (3 mL) to give after chromatography (CH_2Cl_2/EtOAc 1:9) oxazolidinone **12a** (55 mg, 25%) and oxazolidinone **12b** (55 mg, 25%).

12a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.45–7.25 (m, 5H, H_{ar}); 5.22 (q, 1H, CH_3CHN, *J*=7.3); 4.83 (d, 1H, 2-H, $J_{2\text{-}3}$=8.3); 4.47 (dd, 1H, 4a-H, $J_{4a\text{-}4b}$=10.6, $J_{4a\text{-}3}$=1.5); 4.34 (dd, 1H, 4b-H, $J_{4b\text{-}4a}$=10.6, $J_{4b\text{-}3}$=5.1); 4.22 (ddd, 1H, 3-H, $J_{3\text{-}2}$=8.3, $J_{3\text{-}4b}$=5.1, $J_{3\text{-}4a}$=1.5); 1.68 (d, 3H, CH_3CHN, *J*=7.3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.5 (C-1); 155.9 (C=O); 137.6 (Cq_{ar}); 129.2 (C_{ar}); 128.7 (C_{ar}); 127.2 (C_{ar}); 71.3 (C-4); 69.8 (C-2); 54.1 (C-3); 53.5 (CH_3CH); 18.6 (CH_3CH). $[\alpha]_D^{20}$ +0.9 (*c* 1.0, $CHCl_3$). HRMS *m*/*z*: calcd for $C_{13}H_{14}NO_4$ $[M+H]^+$: 248.0935; found: 248.0923.

12b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.45–7.3 (m, 5H, H_{ar}); 5.21 (q, 1H, CH_3CHN, *J*=7.1); 4.95 (d, 1H, 2-H, $J_{2\text{-}3}$=8.3); 4.62 (ddd, 1H, 3-H, $J_{3\text{-}2}$=8.3, $J_{3\text{-}4a}$=5.1, $J_{3\text{-}4b}$=1.4); 3.96 (dd, 1H, 4a-H, $J_{4a\text{-}4b}$=10.9, $J_{4a\text{-}3}$=5.1); 3.47 (dd, 1H, 4b-H, $J_{4b\text{-}4a}$=10.9, $J_{4b\text{-}3}$=1.4); 1.67 (d, 3H, CH_3CHN, *J*=7.1). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.4 (C-1); 155.7 (C=O); 138.9 (Cq_{ar}); 129.3 (C_{ar}); 128.8 (C_{ar}); 127.0 (C_{ar}); 69.9 (C-2); 69.8 (C-4); 53.5 (C-3); 52.7 (CH_3CH); 15.7 (CH_3CH). $[\alpha]_D^{20}$ −180.8 (*c* 0.9, $CHCl_3$). HRMS *m*/*z*: calcd for $C_{13}H_{14}NO_4$ $[M+H]^+$: 248.0929; found: 248.0923.

*4.2.8. (3aS,6S,6aS)-6-Ethyltetrahydrofuro[3,4-d]oxazol-2(3H)-one ((+)-**9**).* The protocol used for the synthesis of **9** was applied to PMB-protected compound (+)-**8** (41 mg, 0.093 mmol) and CAN (310 mg, 0.56 mmol) in CH_3CN/H_2O (9:1) (3 mL) to give the compound (+)-**9** (20 mg, 66%). All analyses were in agreement with the data reported in the literature.[8d] $[\alpha]_D^{20}$ +65.0 (*c* 0.8, $CHCl_3$) [Lit.[8d] $[\alpha]_D^{20}$ +66.5 (*c* 1.2, $CHCl_3$)].

4.2.9. (2S,3S,4S)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (jaspine B). The protocol used for the synthesis of racemic jaspine B was applied to oxazolidinone (+)-**9** (20 mg, 0.062 mmol) and KOH (34.5 mg, 0.62 mmol) in EtOH/H_2O (8:2) (1.5 mL) to give jaspine B (17 mg, 92%). All analyses were in agreement with the data reported in the literature.[8d] $[\alpha]_D^{20}$ +18.8 (*c* 0.85, EtOH) [Lit.[1] $[\alpha]_D^{20}$ +18 (*c* 0.1, EtOH)].

*4.2.10. (3aR,6R,6aR)-6-Ethyltetrahydrofuro[3,4-d]oxazol-2(3H)-one ((−)-**9**).* The protocol used for the synthesis of **9** was applied to PMB-protected compound (−)-**8** (41 mg, 0.093 mmol) and CAN (310 mg, 0.56 mmol) in CH_3CN/H_2O (9:1) (3 mL) to give the compound (−)-**9** (20 mg, 66%). NMR spectral data and mass spectroscopy were identical to those of compound (+)-**9**. $[\alpha]_D^{20}$ −65.7 (*c* 1.0, $CHCl_3$).

4.2.11. (2R,3R,4R)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (ent-jaspine B). The protocol used for the synthesis of jaspine B was applied to oxazolidinone (−)-**9** (20 mg, 0.062 mmol) and KOH (34.5 mg, 0.62 mmol) in EtOH/H_2O (8:2) (1.5 mL) to give *ent*-jaspine B (16 mg, 87%). NMR spectral data and mass spectroscopy were

identical to those of jaspine B. $[\alpha]_D^{20}$ −19.0 (*c* 0.8, EtOH) [Lit.[10c] $[\alpha]_D^{20}$ −17.7 (*c* 0.4, EtOH)].

4.3. Separation of enantiomers of (±)-8

Chemicals. Solvents used were HPLC grade methanol (MeOH) and dichloromethane (CH_2Cl_2) provided by Carlo Erba Reagents (France). Carbon dioxide was provided by Linde (France).

Samples preparation. 58 mg in 2.0 mL of CH_2Cl_2, the concentration was 30 g/L.

Apparatus and operating conditions. The separation of both enantiomers and the analysis of purified fractions were carried out using manufactured equipment with three model HPLC K-501 Knauer pumps, two used for carbon dioxide and one for the modifier. Control of the mobile phase composition was performed by the modifier pump. The pump head used for pumping the carbon dioxide was cooled to −10 °C by a cryostat (Minichiller, Huber). The injector valve was supplied with a 50 μL loop. The autosampler HT300L allowed from 1 to 500 μL injection volumes. The columns were thermostated by an oven regulated at 35 °C. A Chiralpak IC column (5 μm silica particles immobilized with cellulose tris-(3,5-dichlorophenylcarbamate), 250×4.6 mm for analytical scale and 250×10 mm for preparative scale) was used with a 25% of a CH_2Cl_2/MeOH mixture (80:20, v/v) as an additive in a CO_2 mobile phase. The flowrate was 4 mL for analytical scale and 12 mL/min for preparative scale and the outlet pressure was 100 bars.

The detector was Smartline UV 2600 Knauer detector. UV detection was carried out at 270 nm. Injection volumes were 10 μL for analytical scale and 50 μL for preparative scale.

Both isomers were obtained with an enantiomeric purity superior to 99.5% in the re-analysis (see ESD) and in 80% yield (23 mg).

4.4. Biological evaluation

For cytotoxicity evaluation, 3000 cells (HCT116, GM637H or U2OS) were seeded per wells in 96-wells plates and, 24 h later, were treated with concentrations ranging from 10 nM to 50 μM (8 replicates for each) for jaspine B and from 175 nM to 100 μM (8 replicates for each) for *ent*-jaspine B. After 4 days of treatment, cells were incubated with the cell proliferation reagent WST-1 (Roche) for 3-4 h and the absorbance was then measured with a scanning multi-well spectrophotometer at 450 nm. The measured absorbance directly correlates to the number of viable cells. Data were analyzed using Prism softwares.

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The biological evaluations were carried out by the Platform of biological activities evaluation at ITAV-USR35005, Centre Pierre Potier in Toulouse.

Supplementary data

Copies of ^1H and ^{13}C NMR spectra of new compounds, supplementary crystallographic data and analytical chiral HPLC chromatograms. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.06.091.

References and notes

1. Kuroda, I.; Musman, M.; Ohtani, I. I.; Ichiba, T.; Tanaka, J.; Gravalos, D. G.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1505–1506.
2. Ledroit, V.; Debitus, C.; Lavaud, C.; Massiot, G. *Tetrahedron Lett.* **2003**, *44*, 225–228.
3. Salma, Y.; Lafont, E.; Therville, N.; Carpentier, S.; Bonnafe, M. J.; Levade, T.; Génisson, Y.; Andrieu-Abadie, N. *Biochem. Pharmacol.* **2009**, *78*, 477–485.
4. (a) Canals, D.; Mormeneo, D.; Fabrias, G.; Llebaria, A.; Casas, J.; Delgado, A. *Bioorg. Med. Chem.* **2009**, *17*, 235–241; (b) Yoshimitsu, Y.; Oishi, S.; Miyagaki, J.; Inuki, S.; Ohno, H.; Fujii, N. *Bioorg. Med. Chem.* **2011**, *19*, 5402–5408; (c) Yoo, H.; Lee, Y. S.; Lee, S.; Kim, S.; Kim, T. Y. *Phytother. Res.* **2012**, *26*, 1927–1933.
5. Shin, D. H.; Kim, T. Y. U.S. Patent, US 2012/0071424 A1, 2012.
6. For reviews see: (a) Abraham, E.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2008**, *19*, 1027–1047; (b) Ballereau, S.; Baltas, M.; Génisson, Y. *Curr. Org. Chem.* **2011**, *15*, 953–986.
7. (a) Inuki, S.; Yoshimitsu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2009**, *11*, 4478–4481; (b) Urano, H.; Enomoto, M.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 152–157; (c) Inuki, S.; Yoshimitsu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3831–3842; (d) Vichare, P.; Chattopadhyay, A. *Tetrahedron: Asymmetry* **2010**, *21*, 1983–1987; (e) Srinivas Rao, G.; Venkateswara Rao, B. *Tetrahedron Lett.* **2011**, *52*, 6076–6079; (f) Passiniemi, M.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2011**, *9*, 1774–1783; (g) Yoshimitsu, Y.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3843–3846; (h) Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Eur. J. Org. Chem.* **2011**, 1514–1519; (i) Bae, H.; Jeon, H.; Baek, D. J.; Lee, D.; Kim, S. *Synthesis* **2012**, *44*, 3609–3612; (j) Yoshimitsu, Y.; Miyagaki, J.; Oishi, S.; Fujii, N.; Ohno, H. *Tetrahedron* **2013**, *69*, 4211–4220; (k) Srinivas Rao, G.; Chandrasekhar, B.; Venkateswara Rao, B. *Tetrahedron: Asymmetry* **2012**, *23*, 564–569.
8. (a) Chandrasekhar, S.; Tiwari, B.; Prakash, S. J. *Arkivoc* **2006**, 155–161; (b) Génisson, Y.; Lamande, L.; Salma, Y.; Andrieu-Abadie, N.; Andre, C.; Baltas, M. *Tetrahedron: Asymmetry* **2007**, *18*, 857–864; (c) Rives, A.; Ladeira, S.; Levade, T.; Andrieu-Abadie, N.; Génisson, Y. *J. Org. Chem.* **2010**, *75*, 7920–7923; (d) Salma, Y.; Ballereau, S.; Maaliki, C.; Ladeira, S.; Andrieu-Abadie, N.; Génisson, Y. *Org. Biomol. Chem.* **2010**, *8*, 3227–3243; (e) Ballereau, S.; Andrieu-Abadie, N.; Saffon, N.; Génisson, Y. *Tetrahedron* **2011**, *67*, 2570–2578; (f) Jeon, H.; Bae, H.; Baek, D. J.; Kwak, Y.-S.; Kim, D.; Kim, S. *Org. Biomol. Chem.* **2011**, *9*, 7237–7242; (g) Salma, Y.; Ballereau, S.; Ladeira, S.; Lepetit, C.; Chauvin, R.; Andrieu-Abadie, N.; Génisson, Y. *Tetrahedron* **2011**, *67*, 4253–4262.
9. (a) Jayachitra, G.; Sudhakar, N.; Anchoori, R. K.; Rao, B. V.; Roy, S.; Banerjee, R. *Synthesis* **2010**, 115–119; (b) Sudhakar, N.; Kumar, A. R.; Prabhakar, A.; Jagadeesh, B.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 325–327; (c) Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sanchez-Fernandez, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510–2513; (d) van den Berg, R.; Boltje, T. J.; Verhagen, C. P.; Litjens, R.; van der Marel, G. A.; Overkleeft, H. S. *J. Org. Chem.* **2006**, *71*, 836–839; (e) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sanchez-Fernandez, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665–1673; (f) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sanchez-Fernandez, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 4668; (g) Reddipalli, G.; Venkataiah, M.; Mishra, M. K.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2009**, *20*, 1802–1805; (h) Sanchez-Eleuterio, A.; Quintero, L.; Sartillo-Piscil, F. *J. Org. Chem.* **2011**, *76*, 5466–5471; (i) Lee, D. *Synlett* **2012**, 2840–2844.
10. (a) Ramana, C. V.; Giri, A. G.; Suryawanshi, S. B.; Gonnade, R. G. *Tetrahedron Lett.* **2007**, *48*, 265–268; (b) Cruz-Gregorio, S.; Espinoza-Rojas, C.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2011**, *52*, 6370–6371; (c) Prasad, K. R.; Penchalaiah, K. *Tetrahedron: Asymmetry* **2011**, *22*, 1400–1403.
11. (a) Valle, M. S.; Saraiva, M. F.; Retailleau, P.; de Almeida, M. V.; Dodd, R. H. *J. Org. Chem.* **2012**, *77*, 5592–5599; (b) Dauban, P.; de Saint-Fuscien, C.; Dodd, R. H. *Tetrahedron* **1999**, *55*, 7589–7600; (c) Dubois, L.; Mehta, A.; Tourette, E.; Dodd, R. H. *J. Org. Chem.* **1994**, *59*, 434–441.
12. (a) Tarrade, A.; Dauban, P.; Dodd, R. H. *J. Org. Chem.* **2003**, *68*, 9521–9524; (b) Tarrade-Matha, A.; Valle, M. S.; Tercinier, P.; Dauban, P.; Dodd, R. H. *Eur. J. Org. Chem.* **2009**, 673–686; (c) Valle, M. S.; Tarrade-Matha, A.; Dauban, P.; Dodd, R. H. *Tetrahedron* **2008**, *64*, 419–432.
13. Stankovic, S.; D'Hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643–665.
14. Sim, T. B.; Kang, S. H.; Lee, K. S.; Lee, W. K.; Yun, H.; Dong, Y. K.; Ha, H. J. *J. Org. Chem.* **2003**, *68*, 104–108.
15. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178.
16. (a) Gueyrard, D.; Haddoub, R.; Salem, A.; Bacar, N. S.; Goekjian, P. G. *Synlett* **2005**, 520–522; (b) Bourdon, B.; Corbet, M.; Fontaine, P.; Goekjian, P. G.; Gueyrard, D. *Tetrahedron Lett.* **2008**, *49*, 747–749; (c) Tomas, L.; Bourdon, B.; Caille, J. C.; Gueyrard, D.; Goekjian, P. G. *Eur. J. Org. Chem.* **2013**, 915–920.
17. Pospisil, J. i.; Sato, H. *J. Org. Chem.* **2011**, *76*, 2269–2272.
18. The stereochemistry of the double bond was established by analogy with compounds described in the literature (Ref. 7c).
19. Tomas, L.; Boije af Gennäs, G.; Hiebel, M. A.; Hampson, P.; Gueyrard, D.; Pelotier, B.; Yli-Kauhaluoma, J.; Piva, O.; Lord, J. M.; Goekjian, P. G. *Chem.—Eur. J.* **2012**, *18*, 7452–7466.
20. Tomas, L.; Gueyrard, D.; Goekjian, P. G. *Tetrahedron Lett.* **2010**, *51*, 4599–4601.
21. Taylor, L. T. *J. Supercrit. Fluids* **2009**, *47*, 566–573.
22. Miller, L.; Potter, M. *J. Chromatogr., B* **2008**, *875*, 230–236.
23. Ren-Qi, W.; Teng-Teng, O.; Siu-Choon, N.; Weihua, T. *TrAC, Trends Anal. Chem.* **2012**, *37*, 83–100.
24. (a) SAINT-NT; Bruker AXS: Madison, W; (b) SADABS, P. f. d. c., Bruker-AXS.
25. Sheldrick, G. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.