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Stereoselective synthesis of jaspine B from D-xylose

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Abstract—The natural cytotoxic marine compound, jaspine B, is stereoselectively synthesized from D-xylose in 11 linear steps with a 23.9% overall yield. The key step in the synthesis involves an iodine-induced debenzylation of a primary alcohol and the subsequent 2,5-cyclization to fit the required configuration of jaspine B. A preliminary bioassay shows strong inhibition activities against human MDA231, Hela, and CNE cell lines, indicating potential usage in various cancer treatments.

Keywords: Natural products; Jaspine B; Antitumor activity; Carbohydrates; Total synthesis

1. Introduction

Phytosphingosine is involved in several biological processes, including heat–stress response and endocytic events.[1] Further studies revealed that sphingosine 1-phosphate induces a rapid and relevant release of arachidonic acid, and increases phospholipase D activity in A549 cells.[2] Phytosphingosine is also found to be a key intermediate from which more complex metabolites are derived.[3] Apart from the linear structures, phytosphingosine derivatives also exist as anhydro forms that were shown to be potent inhibitors of a variety of glycosidase activities.[4] Jaspine B (**1**, Scheme 1), one of the natural occurring anhydrophytosphingosine derivatives, was isolated from marine sponges, *Pachastrissa* sp. and *Jaspis* sp.,[5] and exhibited a significant cytotoxicity against P388, A549, HT29, and MEL28 carcinoma cell lines in vitro.[6] High-resolution NMR and mass spectral analyses, as well as chemical derivatization studies suggested an all-syn trisubstituted tetrahydrofuran framework, and the (2*S*,3*S*,4*S*) absolute configuration of jaspine B. The impressive biological activity and novel structural features have encouraged several research groups to explore the preparation of this compound.[7] To improve our understanding of this anhydrosphingosine and its targeting to tumor cells and to lay the groundwork for more potent analogues based on this novel structure, we launched a stereoselective total synthesis of natural jaspine B. We report herein a practical synthesis of jaspine B using D-xylose as the chiral starting material, and a preliminary bioassay against human MDA231, Hela, and CNE cell lines.

2. Results and discussion

We have previously accomplished the total synthesis of jaspine B.[7d] To provide more samples for bioactivity research, we enlarged the reaction scale (10 g) and unexpectedly found that the conversion of mesylate into azido intermediate in the presence of C-1 diethylacetal group was quite slow. To explore a more practical method toward jaspine B preparation, we designed the following strategy as shown in Scheme 1.

3,5-Di-*O*-benzyl-α-D-xylofuranose (**3**) was easily obtained from D-xylose (**2**) through a three-step reaction in a 72% overall yield.[8] Oxidation of diol **3** with $NaIO_4$

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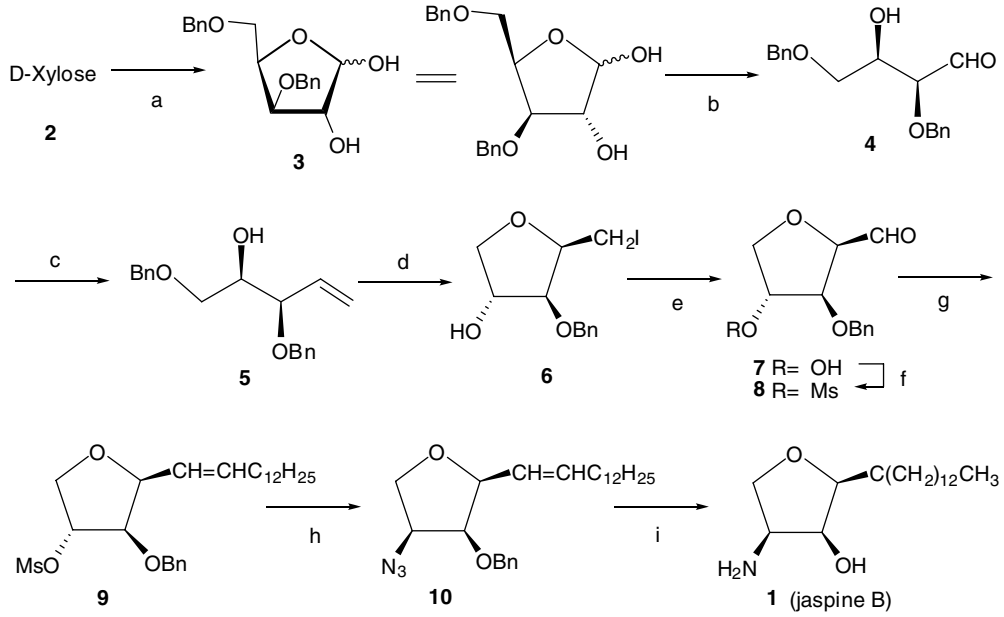

Scheme 1. Total synthesis of jaspine B. Reagents and conditions: (a) Ref. 8, 72% in three steps; (b) $NaIO_4$, MeOH, H_2O; (c) $CH_3Ph_3P^+Br^-$, BuLi, dry THF, −40 °C to rt, 82% for two steps; (d) I_2, $NaHCO_3$, CH_3CN, 80%; (e) $NaHCO_3$, dry DMSO, 150 °C, 6 min; (f) MsCl, Py, rt, 30 min, 74% for two steps; (g) $C_{13}H_{27}Ph_3P^+Br^-$, BuLi, dry THF, −40 °C to rt, 90%, *Z*/*E* ratio >10/1; (h) NaN_3, NH_4Cl, DMF, 120 °C, 20 h, 80%; (i) Pd/C, H_2, MeOH, TFA, 5 h, 95%.

in methanol[9] gave (2*S*,3*R*)-2,4-bis(benzyloxy)-3-hydroxybutanal (**4**), which was directly subjected to a Wittig reaction with $Ph_3P{=}CH_2$ and gave (2*R*,3*R*)-1,3-di-*O*-benzyl-4-pentene-1,2,3-triol (**5**) in an 82% yield (Scheme 1). An iodine-induced consecutive cyclization/benzyl deprotection was carried out smoothly in anhyd acetonitrile in the presence of I_2 and $NaHCO_3$,[10] affording iodide **6** (80%), which was further transformed into (2*R*,3*S*,4*R*)-3-(benzyloxy)-4-hydroxytetrahydrofuran-2-carbaldehyde (**7**) with dimethyl sulfoxide.[11] On treatment of crude **7** with methanesulfonyl chloride in pyridine we obtained (2*R*,3*S*,4*R*)-3-(benzyloxy)-4-methanesulfonyloxytetrahydrofuran-2-carbaldehyde (**8**) in a 74% isolated yield. The standard Wittig olefination of **8** with a C-13 alkyl donor resulted in the incorporation of an inseparable mixture of (3*R*,4*R*,5*S*)-4-(benzyloxy)-5-((*E*,*Z*)-tetradec-1-enyl)tetrahydrofuran-3-yl methanesulfonate (**9**, 90% yield) with the corresponding C-14 olefinic side chain. The *Z*/*E* ratio was determined to be greater than 10:1 based on ^1H NMR spectroscopy, but both could be further reduced to the desired alkyl side chain. The S_N2 substitution of **9** with NaN_3 in DMF gave (2*S*,3*S*,4*S*)-4-azido-3-(benzyloxy)-2-((*E*,*Z*)-tetradec-1-enyl)tetrahydrofuran (**10**) in an 80% yield. A single step hydrogenation of the azido and benzyl groups, and the side-chain double bond in methanol (containing 1% TFA) furnished target molecule, jaspine B (**1**), in a salt form in an excellent yield of 95%.

The effects of jaspine B against human MDA231, CNE, and Hela cell growth were investigated based on Higa's method.[6a] Jaspine B significantly inhibited the proliferation of human MDA231 cell lines with IC_{50} 0.52, 0.37, and 0.1 μg/mL corresponding to the treatments of 24, 48, and 72 h, respectively. For human CNE cell lines, the IC_{50}s were 0.78 and 0.005 μg/mL corresponding to 48 and 72 h, while human Hela cell lines had an IC_{50} 0.79 μg/mL at 72 h. The results are summarized in Table 1.

In conclusion, utilizing a chiral-pool strategy based on D-xylose as the starting material, the stereoselective total synthesis of a structurally unique bioactive anhydrosphingosine natural product, jaspine B, has been

Table 1. Effect (inhibition rate, %) of jaspine B on the growth of human MDA231, CNE, and HeLa cells

Groups	Dose (μg/mL)	MDA231			Hela			CNE		
		24 h	48 h	72 h	24 h	48 h	72 h	24 h	48 h	72 h
Jaspine B	0.005	16	26	37	4	0	42	0	0	49
	0.01	12	35	44	0	17	45	0	19	69
	0.1	35	32	51	20	27	42	0	23	73
	1	67	93	95	45	35	52	43	59	86
CDDP	3	35	28	32	27	15	59	0	37	68
Control	0	0	0	0	0	0	0	0	0	0

achieved in 11 linear steps and a 23.9% overall yield. The key step in the synthesis involves an iodine-induced debenzylation on primary alcohol and the subsequent 2,5-cyclization to fit the required configuration toward jaspine B. A preliminary bioassay shows that jaspine B presents strong inhibition activities against human MDA231, Hela, and CNE cell lines, indicating potential usage in various cancer treatments. The current report provides an alternative way for the preparation of the antitumor agent jaspine B, and the method should be valuable in the preparation of other tetrahydrofuran derivatives.[12]

3. Experimental

3.1. General methods

Optical rotations were determined at 25 °C with a Perkin–Elmer Model 241-Mc automatic polarimeter, and $[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker ARX 400 spectrometer for solutions in $CDCl_3$ or CD_3OD. Chemical shifts are given in parts per million downfield from internal Me_4Si. Mass spectra were measured using a JEOL JMS-700 mass spectrometer. Thin-layer chromatography (TLC) was performed on silica gel HF_{254} with detection by charring with 30% (v/v) H_2SO_4 in MeOH, or in some cases by a UV lamp. Column chromatography was conducted by elution of a column of silica gel (100–200 mesh) with EtOAc–petroleum ether (60–90 °C) as the eluent. Solutions were concentrated at <60 °C under reduced pressure.

3.2. (2*R*,3*R*)-1,3-Di-*O*-benzyl-4-pentene-1,2,3-triol (5)

To a solution of compound **3** (660 mg, 2 mmol) in MeOH (10 mL) was added $NaIO_4$ (642 mg in 5 mL H_2O, 3 mmol). The mixture was stirred at room temperature and monitored by TLC (2:1 petroleum ether–EtOAc) until all starting materials disappeared. The mixture was then filtered, and the filtrate was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phase was dried over anhyd Na_2SO_4 and concentrated to give syrupy (2*S*,3*R*)-2,4-bis(benzyloxy)-3-hydroxybutanal (**4**), which was directly used for the next reaction without purification. To a pre-cooled (−40 °C) solution of Wittig salt $CH_3Ph_3P^+Br^-$ (1.07 g, 3 mmol) in THF (25 mL) was slowly added *n*-BuLi (2.5 M in hexane, 2 mL, 5 mmol) under N_2 protection. The orange mixture was stirred under these conditions for about 20 min, then a solution of the above **4** in dry THF (5 mL) was added dropwise under N_2 protection. The mixture was stirred at this temperature for another 30 min, then allowed to warm up to room temperature. The progress of the reaction was monitored by TLC (2:1 petroleum ether–EtOAc) until all starting materials disappeared. The reaction was quenched by satd NH_4Cl (0.2 mL), then diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over anhyd Na_2SO_4 and concentrated to dryness. Purification of the residue by silica gel column chromatography (3:1 petroleum ether–EtOAc) gave **5** (489 mg, 82% for two steps) as a syrup: $[\alpha]_D^{25}$ −21 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70 (d, 1H, *J* 3.9 Hz), 3.50 (dd, 1H, *J* 5.5, 10.0 Hz), 3.58 (dd, 1H, *J* 3.9, 10.0 Hz), 3.76–3.80 (m, 1H), 3.92 (t, 1H, *J* 6.7 Hz), 4.36, 4.63 (2d, 2H, $J = 11.6$ Hz), 4.50, 4.55 (2d, 2H, $J = 12.0$ Hz), 5.32–5.36 (m, 2H), 5.74–5.83 (m, 1H), 7.25–7.36 (m, 10H). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.81; H, 7.36.

3.3. (2*R*,3*S*,4*R*)-3-Benzyloxy-2-(iodomethyl)tetrahydrofuran-4-ol (6)

To a solution of **5** (220 mg, 0.74 mmol) in anhyd CH_3CN (10 mL) was added $NaHCO_3$ (186 mg, 2.2 mmol). The mixture was stirred at 0 °C for 5 min, and then iodine (560 mg, 2.2 mmol) was added. The reaction was monitored by TLC (2:1 petroleum ether–EtOAc). After completion, the mixture was diluted with EtOAc and washed with aq sodium thiosulfate. The combined organic phase was dried over anhyd Na_2SO_4 and concentrated under vacuum to give a diastereomeric mixtrue. Purification of the mixtures by silica gel column chromatography (2:1 petroleum ether–EtOAc) gave pure compound **6** (197 mg, 80%) as a syrup: $[\alpha]_D^{25}$ +78 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (br s, 1H), 3.28 (dd, 1H, *J* 6.0, 9.3 Hz), 3.36 (t, 1H, *J* 9.3 Hz), 3.82 (d, 1H, *J* 9.9 Hz), 4.00 (d, 1H, *J* 3.7 Hz), 4.20 (dd, 1H, *J* 3.9, 9.9 Hz), 4.39–4.44 (m, 2H), 4.62, 4.67 (2d, 2H, *J* 11.4 Hz), 7.32–7.37 (m, 5H). Anal. Calcd for $C_{12}H_{15}IO_3$: C, 43.13; H, 4.52. Found C, 43.31; H, 4.42.

3.4. (2*R*,3*S*,4*R*)-3-(Benzyloxy)-4-hydroxytetrahydrofuran-2-carbaldehyde (7)

To a mixture of DMSO (5 mL) and $NaHCO_3$ (400 mg) at 150 °C under N_2 protection was added compound **6** (170 mg, 0.51 mmol). The mixture was stirred at 150 °C for 5 min, and then rapidly cooled to room temperature. The mixture was poured into ice water and extracted with Et_2O (3 × 10 mL). The combined organic phase was dried over anhyd Na_2SO_4 and concentrated to dryness. Purification of the residue by silica gel column chromatography (2:1 petroleum ether–EtOAc) gave aldehyde **7**, which was directly used in the next step without further purification. A small sample was purified on a silica gel column to provide analytically pure **7**: $[\alpha]_D^{25}$ +64 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (br s, 1H), 3.95 (d, 1H, *J* 10.0 Hz), 4.28–4.31 (m,

2H), 4.41 (d, 1H, *J* 3.3 Hz), 4.51 (dd, *J* 1.7, 4.9 Hz), 4.53, 4.60 (2d, 2H, *J* 11.9 Hz), 7.25–7.37 (m, 5H), 9.58 (d, 1H, *J* 1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 72.5, 74.4, 75.0, 84.6, 85.9, 127.6, 127.9, 128.4, 136.9, 201.0. HRFABMS: Calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 223.0878 $(M+H)^+$.

3.5. (2*R*,3*S*,4*R*)-3-(Benzyloxy)-4-methanesulfonyloxy-tetrahydrofuran-2-carbaldehyde (8)

To a solution of crude **7** (0.51 mmol) in pyridine (2 mL) was added methanesulfonyl chloride (90 μL, 1.2 mmol). The mixture was stirred at room temperature for 30 min, and then co-evaporated with toluene under vacuum. Purification of the residue by silica gel column chromatography (1:1 petroleum ether–EtOAc) gave **8** (113 mg, 74% for two steps) as a syrup: $[\alpha]_D^{25}$ +27 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 3H), 4.10 (d, 1H, *J* 11.1 Hz), 4.28 (dd, 1H, *J* 3.5, 11.1 Hz), 4.44 (d, 1H, *J* 4.6 Hz), 4.50, 4.60 (2d, 2H, *J* 11.9 Hz), 4.57 (d, 1H, *J* 4.9 Hz), 5.12 (d, 1H, *J* 3.1 Hz), 7.21–7.31 (m, 5H), 9.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.9, 71.8, 72.2, 80.6, 82.9, 83.9, 127.5, 127.9, 128.2, 136.1, 198.7. HRFABMS: Calcd for $C_{13}H_{16}O_6S$: 300.0668; Found: 301.0685 $(M+H)^+$.

3.6. (3*R*,4*R*,5*S*)-4-(Benzyloxy)-5-((*E*,*Z*)-tetradec-1-enyl)-tetrahydrofuran-3-yl methanesulfonate (9)

To a pre-cooled (−40 °C) solution of the Wittig salt $C_{13}H_{27}Ph_3P^+Br^-$ (884 mg, 1.68 mmol) in anhyd THF (25 mL) was slowly added *n*-BuLi (2.5 M in hexane, 0.67 mL, 1.68 mmol) under N_2 protection. The orange solution was stirred under these conditions for about 20 min, and then a solution of **8** (336 mg, 1.12 mmol) in dry THF (3 mL) was added dropwise under N_2 protection. The mixture was stirred at this temperature for another 30 min, and then allowed to warm up to room temperature. The reaction was monitored by TLC (3:1 petroleum ether–EtOAc) until all starting materials disappeared. The reaction was then quenched by satd NH_4Cl (0.2 mL), and the mixture was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over anhyd Na_2SO_4 and concentrated to dryness. Purification of the residue by silica gel column chromatography (3:1 petroleum ether–EtOAc) gave **9** (470 mg, 90%, Z/E >10:1, determined by ^{1}H NMR) as a syrup: Selected ^{1}H NMR (400 MHz, $CDCl_3$) for the *Z*-isomer: δ 0.88 (t, 3H, *J* 7.1 Hz), 1.27 (br s, 20H), 2.07–2.13 (m, 2H), 2.99 (s, 3H), 3.98 (dd, 1H, *J* 1.9, 10.9 Hz), 4.08 (d, 1H, *J* 3.9 Hz), 4.29 (dd, 1H, *J* 4.9, 10.9 Hz), 4.64 (2d, 2H, *J* 12.1 Hz), 4.77 (dd, 1H, *J* 3.9, 8.3 Hz), 5.16 (d, 1H, *J* 4.7 Hz), 5.63–5.77 (m, 2H), 7.29–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 27.9, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 38.3, 70.5, 72.3, 76.0, 82.6, 82.9, 123.3, 127.7, 127.9, 128.4, 135.7, 137.2. Anal. Calcd for $C_{26}H_{42}O_5S$: C, 66.92; H, 9.07. Found: C, 67.15; H, 8.98.

3.7. (2*S*,3*S*,4*S*)-4-Azido-3-(benzyloxy)-2-((E,Z)-tetradec-1-enyl)tetrahydrofuran (10)

To a solution of **9** (47 mg, 0.1 mmol, *Z*, *E* mixture) in dry DMF (5 mL) was added NaN_3 (39 mg, 0.6 mmol) and anhyd NH_4Cl (107 mg, 0.2 mmol). The mixture was heated to 120 °C and stirred for about 20 h in a dark room. The reaction was monitored by TLC (4:1 petroleum ether–EtOAc) until all starting materials disappeared, then the mixture was diluted with water and extracted with EtOAc (4 × 8 mL). The organic phase was dried over anhyd Na_2SO_4 and concentrated. Purification of the residue by silica gel column chromatography (4:1 petroleum ether–EtOAc) gave **10** (33 mg, 80%, *Z*, *E* mixture) as a syrup: Selected ^{1}H NMR (400 MHz, $CDCl_3$) for the *Z* isomer: δ 0.88 (t, 3H, *J* 7.1 Hz), 1.20 (br s, 20H), 2.07–2.09 (m, 2H), 3.88–3.97 (m, 3H), 4.11 (t, 1H, *J* 5.0 Hz), 4.62, 4.70 (2d, 2H, *J* 11.8 Hz), 4.71–4.72 (m, 1H), 5.65–5.73 (m, 2H, *J* 11.0 Hz), 7.29–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 27.7, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 61.5, 68.6, 73.3, 75.8, 80.4, 124.9, 127.7, 127.8, 128.3, 135.0, 137.4. HRFABMS: Calcd for $C_{25}H_{39}N_3O_2$: 413.3042. Found: 414.3068 $(M+H)^+$.

3.8. Synthesis of jaspine B (1)

To a mixture of olefin **10** (210 mg, 0.5 mmol) and Pd/C (10% content, 50 mg) in MeOH (50 mL, containing 1% of TFA) H_2 was bubbled in at a flow rate of 100 mL/min under room temperature and 4 atm pressure. (Caution! Extreme fire hazard!) The hydrogenation was kept at these conditions for about 5 h, at the end of which time, TLC (4:1 EtOAc–MeOH) showed only one product generated. The Pd/C was filtered, and the filtrate was concentrated. The residue was purified on a short silica gel column using 4:1 EtOAc–MeOH as eluent to furnish target compound **1** (145 mg, 95%) as a white solid in salt form: $[\alpha]_D^{25}$ +11 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 0.89 (t, 3H, *J* 7.0 Hz), 1.26–1.45 (m, 24H), 1.60–1.65 (m, 2H), 3.70 (dt, 1H, *J* 3.5, 6.8 Hz), 3.79 (dd, 1H, *J* 4.8, 7.9 Hz), 3.82–3.93 (m, 2H), 4.23 (dd, 1H, *J* 3.5, 4.8 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 14.5, 23.7, 27.2, 29.7, 30.5, 30.7, 30.8, 30.9, 33.1, 54.3, 68.9, 70.9, 84.4. HRFABMS: Calcd for $C_{18}H_{37}NO_2$ (after co-evaporation with NH_4OH): 299.2824. Found: 300.2856 $(M+H)^+$.

3.9. Bioassay

Human MDA231, CNE, and HeLa cells (3×10^5/well) were cultured in a suspension of Dulbcco's Modified

Eagle Medium (DMEM) supplemented with 10% newborn calf serum, 100 kU/mL of penicillin and 100 mg/mL of streptomycin in a humidified atmosphere of 5% CO_2 at 37 °C. Exponentially growing tumor cells at 1×10^5 cells/mL in culture were treated with jaspine B at a concentration of 0.005, 0.01, 0.1, and 1 μg/L for 24, 48, and 72 h, respectively. The positive control cultures were treated with CDDP at 3 μg/mL under the same conditions, while the negative control cultures (DMEM) were left untreated at 37 °C for the same period of time. The number of viable cells was determined by the acid phosphatase assay (APA), and the percentage inhibition of cell proliferation was calculated by the following formula: Inhibition % = [1 − ($OD_{405\,nm}$ for experimental group/$OD_{405\,nm}$ for control group)] × 100%.

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Supplementary data

Supplementary data (images of NMR spectra for compounds) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.08.011.

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