Pergamon

PII: S0031-9422(97)00512-8

Phytochemistry, Vol. 47, No. 1, pp. 31–35, 1998

Printed in Great Britain
0031-9422/98 $19.00+0.00

ANCISTROBERTSONINE A AND RELATED NAPHTHYLISOQUINOLINE ALKALOIDS FROM *ANCISTROCLADUS ROBERTSONIORUM**†

GERHARD BRINGMANN‡, FRIEDRICH TELTSCHIK, MANUELA SCHÄFFER, RENÉ HALLER§, SABINE BÄR§, S. ANNE ROBERTSON¶ and MOHAMMED A. ISAHAKIA‖

Institut für Organische Chemie der Universität, Am Hubland, D-97074 Würzburg, Germany; §Baobab Farm Ltd., P.O. Box 819995, Mombasa, Kenya; ¶P.O. Box 162, Malindi, Kenya; ‖National Museum of Kenya, P.O. Box 40658, Nairobi, Kenya

(*Received in revised form* 6 *April* 1997)

Key Word Index—*Ancistrocladus robertsoniorum*; Ancistrocladaceae; stems; ancistrobertsonine A; ancistrocladine; hamatine; ancistrobrevine B; naphthylisoquinoline alkaloids; High Speed Countercurrent Chromatography (HSCCC); structural elucidation.

Abstract—From the as yet unexplored East African Liana, *Ancistrocladus robertsoniorum*, several naphthylisoquinoline alkaloids have been isolated, based mainly on High Speed Countercurrent Chromatography (HSCCC). The structure of the new compound, ancistrobertsonine A, was elucidated by chemical and spectroscopic methods. Furthermore, the known alkaloids ancistrocladine, its atropo-diastereomer, hamatine, and its regioisomer, ancistrobrevine B, were isolated. © 1997 Elsevier Science Ltd

INTRODUCTION

Ancistrocladus robertsoniorum is one of the most recently discovered members of the Ancistrocladaceae [2], a small monogeneric plant family consisting of nearly 30 species of tropical lianas and shrubs. Although discovered in 1953 in one of the few remaining coastal forests of Kenya, near Mombasa, it was only scientifically described in 1984 [3] and cultivated a few years later [4]. The family Ancistrocladaceae is a rich source of interesting natural products, the naphthylisoquinoline alkaloids [5], which have so far been isolated only from this family and the closely related Dioncophyllaceae. The alkaloids of Asian *Ancistrocladus* species, which produce Ancistrocladaceae-type alkaloids (*S*-configured at C-3 and OR at C-6), vary significantly from those of West and Central African ones, which contain both Dioncophyllaceae- (3*R*-configured and 6-unsubstituted) and Ancistrocladaceae-type alkaloids, as well as their hybrid-type permutations. Therefore, a phytochemical investigation of *A. robersoniorum* should be a rewarding goal, given the central geographic position of this (as yet) only East African *Ancistrocladus* species. Recently, we have reported *A. robertsoniorum* to form crystalline droserone (**1**) when wounded, the quality of the 'biogenic' crystals even being sufficient for an X-ray structural analysis [6, 7]. Except for the identification of this naphthoquinone, which can be regarded as an oxidized form of the naphthalene moiety of naphthylisoquinoline alkaloids, no systematic phytochemical studies have so far been performed on *A. robertsoniorum*. In the present paper, we report on the first application of High Speed Countercurrent Chromatography (HSCCC) in the field of *Ancistrocladus* alkaloids, leading to the isolation of a new naphthylisoquinoline alkaloid, named ancistrobertsonine A (**2**), as well as the known related compounds, ancistrocladine (**3a**), hamatine (**3b**) and ancistrobrevine B (**4**). These natural products provide first hints of the geotaxonomic position of this interesting plant species.

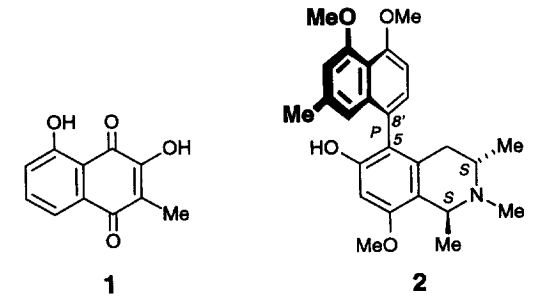
RESULTS AND DISCUSSION

Ancistrocladus robertsoniorum was collected in Kenya in November 1992. Using a mixture of 1 N sulphuric acid–methanol (5:1) [8], the air-dried and ground plant material (stems and twigs) was extracted exhaustively. After evaporation of methanol, prefractionation by liquid–liquid partition with *n*-hexane and chloroform, and addition of ammonia (to give

* Part 94 in the series 'Acetogenic isoquinoline alkaloids'. For Part 93, see ref. [1].

† Dedicated to Prof. Waldemar Adam, on the occasion of his 60th birthday.

‡ Author to whom correspondence should be addressed.



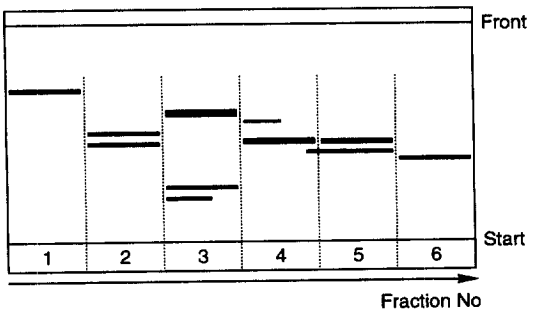
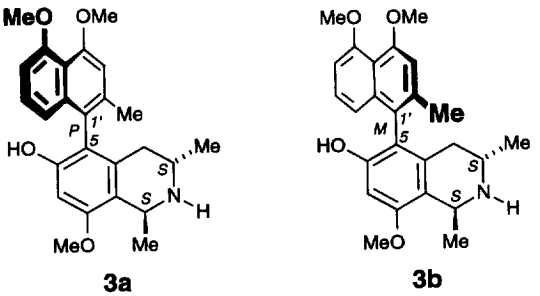


Fig. 2. TLC comparison [silica gel, $CHCl_3$–MeOH (19:1)] of the alkaloid-containing HSCCC fractions.



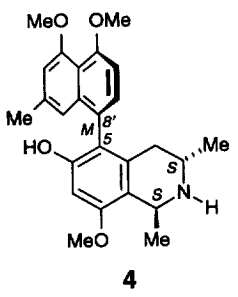


Fig. 1. Natural products of *A. robertsoniorum*.

pH 8), the most polar components were removed from the aqueous phase by extraction with *n*-butanol. The remaining aqueous solution, containing inorganic salts, mainly ammonium sulphate, was discarded. ^{1}H NMR and Dragendorff's test showed only the chloroform fraction to contain alkaloids. The resolution of this complex mixture was achieved, here for the first time for naphthylisoquinoline alkaloids, using the efficient method of HSCCC, a more advanced type of Centrifugal Partition Chromatography (CPC) previously applied [9]. As the eluent, the solvent system chloroform–methanol–0.1 M HCl (5:5:3) [10] was used. The lower organic phase was chosen to be the mobile phase, the elution therefore being done in the (H) → T (Lo) mode [10, 11]. The use of 0.1 M HCl in the solvent system [10, 12] proved to be essential for the separation. During the separation, portions of 4 ml were taken and monitored by TLC (Fig. 2) showing a good pre-separation, in particular, with respect to compounds virtually identical on silica gel. HSCCC fractions of comparable composition were combined, to give a total of six alkaloid-containing fractions.

The alkaloids were further resolved by preparative TLC (HSCCC fractions 3 and 4) or HPLC (fraction 5). Their ^{1}H NMR spectra showed the typical resonances of naphthylisoquinoline alkaloids.

The major compound from fraction 4 proved to be ancistrobrevine B (**4**), a 5,8′-coupled alkaloid previously isolated from *A. abbreviatus* [13]. Its structure was fully confirmed by spectroscopic, chiroptical and degradative methods.

The main alkaloid from the third HSCCC fraction, however, proved to be a novel naphthylisoquinoline alkaloid, subsequently named ancistrobertsonine A. Its ^{1}H NMR spectrum is very similar to that of ancistrobrevine B (**4**). Like in **4** [13], no high-field shift is observed for the signals of Me-2′ (δ 2.34), MeO-4′ (δ 3.94) and MeO-5′ (δ 3.98) [Fig. 3(a)], indicating that none of these groups is in the direct proximity of the biaryl axis, which is fully confirmed by NOE experiments [Fig. 3(b)]. These observations and the spin-system pattern hint at an 8′-position of the biaryl axis in the naphthalene part. A sharp singlet at δ 2.54 indicates the presence of an *N*-methylated tetrahydroisoquinoline. NOE interactions of MeO-8 (δ 3.87) with both Me-1 (δ 1.56) and H-7 (δ 6.53) [Figs 3(a) and (b)] exclude the biaryl axis to be situated in the 7-position. The up-field shift of H_{eq}-4 and H_{ax}-4 (δ 1.94 and 2.43) indicate that these protons are near to the biaryl axis, which must be located at C-5. This is further confirmed by HMBC (H,C Heteronuclear Multiple Bond Correlation) cross-peaks of H-7 (of the isoquinoline part) and H-7′ (of the naphthalene moiety) with the same carbon atom, C-5 [Fig. 3(b)], only possible in a 5,8′-linked naphthylisoquinoline alkaloid. These spectral data and a series of further HMBC interactions (data not shown) establish the basic structure of ancistrobertsonine A as an *N*-methylated, 5,8′-coupled naphthylisoquinoline with the constitution shown in Figs 3(a) and (b).

From further NOE experiments [Fig. 3(c)], the relative configuration at the three stereogenic elements, the centres and the axis, was established. The *trans*-configuration at C-1 *vs* C-3 was determined by a clear NOE interaction between H_{ax}-3 and the likewise axial methyl substituent at C-1. The latter gave a weak,

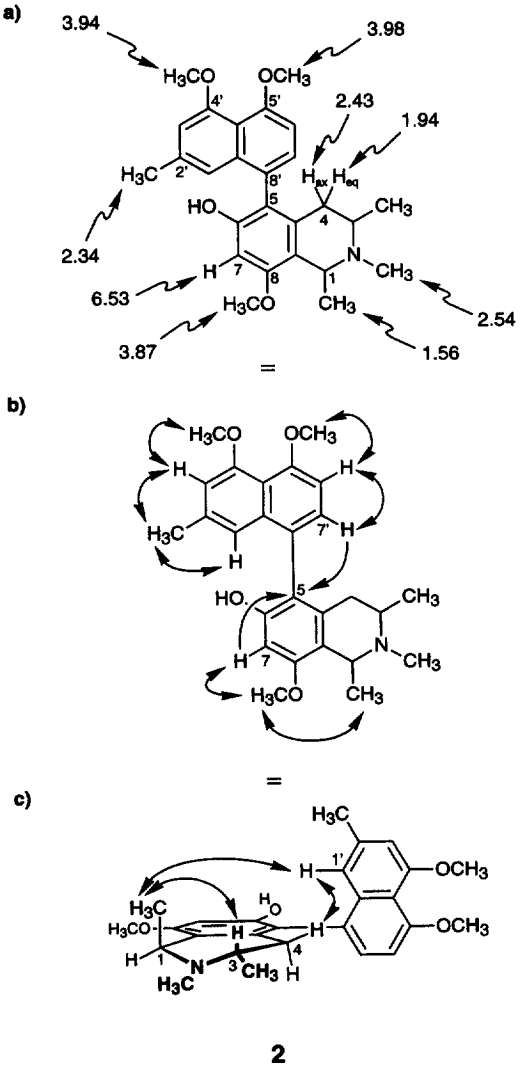


Fig. 3. Constitution **2** of ancistrobertsonine A from (a) selected ^{1}H NMR chemical shifts (δ values in ppm), as well as, (b) NOE and relevant HMBC interactions; its relative stereostructure, (c) by further characteristic NOE interactions.

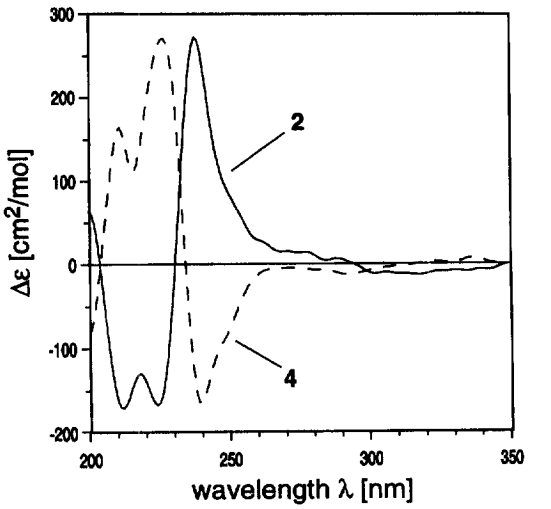


Fig. 4. CD spectra of ancistrobertsonine A (**2**) and ancistrobrevine B (**4**).

but significant NOE interaction with H-1′ [Fig. 3(c)], indicating both spin-systems to be on the same side of the molecule, which was further confirmed by the (stronger) interaction between H-1′ and H_{eq}-4 [Fig. 3(c)].

The absolute configuration at C-1 and C-3 was determined using the ruthenium-mediated oxidative degradation [14], which was recently improved significantly [15]. The resulting 3-(*N*-methylamino) butyric acid and *N*-methylalanine and their *N*-demethylated analogues (as arising from additional *C,N* bond cleavage), were stereochemically analysed by GC-MSD (Gas Chromatography Mass Sensitive Detector), after transformation into their Mosher derivatives. From the *S*-configuration of both amino acids formed, ancistrobertsonine A was attributed to be *S*-configured at the two stereocentres, and given the relative configuration at centres and axis as established above [Fig. 3(c)]; the axial configuration clearly has to be *P*. This is further corroborated by the CD spectrum of the new alkaloid (Fig. 4), which is, as expected, virtually opposite to the one of the *M*-configured alkaloid, ancistrobrevine B (**4**).

Thus, ancistrobertsonine A can unambiguously be attributed the absolute stereostructure **2** with the 1*S*,3*S*,5*P*-configuration; it is the *N*-methylated 5-epimer of ancistrobrevine B (**4**). Compound **2** is the first *trans*-configured Ancistrocladaceae-type naphthylisoquinoline alkaloid with an *N*-methyl-group. Only *N*-methyldioncophylline A (i.e. a Dioncophyllaceae-type alkaloid) has, as yet, this structural feature [16].

The two naphthylisoquinoline alkaloids from fraction 5 (Fig. 2) were identified as ancistrocladine (**3a**) and hamatine (**3b**), by means of analytic HPLC and coelution with authentic samples of synthetic [17, 18] and natural [13] origin. The preparative resolution of this mixture, however, caused severe problems due to the largely dominating presence of hamatine, but was achieved by preparative HPLC on a *ca* 40 mg scale.

During the current investigation, a new and three known naphthylisoquinoline alkaloids were isolated, ancistrobertsonine A (**2**), ancistrocladine (**3a**), hamatine (**3b**) and ancistrobrevine B (**4**). All of these compounds are *S*-configured at C-3 and bear an oxygen function at C-6 and, thus, represent pure 'Ancistrocladaceae-type' naphthylisoquinoline alkaloids. In this respect, *A. robertsoniorum* from East Africa resembles the Asian *Ancistrocladus* species, which, without any exception, have been found to produce Ancistrocladaceae-type alkaloids, while all the Central and West African *Ancistrocladus* species investigated so far, have likewise been found to produce Dioncophyllaceae- and hybrid-type alkaloids. On the other hand, the identification of 5,8′-coupled alkaloids (*viz.* **2** and **4**), which have never been isolated from Asian species, reveals a clear taxonomic relationship to West and Central African *Ancistrocladus* species.

Thus, *A. robertsoniorum* comprises significant characteristics of both African and Asian *Ancistrocladus* species and can therefore be regarded as a 'geotaxonomic' link between the African and the Asian representatives of the Ancistrocladaceae.

EXPERIMENTAL

General. Mps uncorr. Optical rotations: 25°, 10 cm cell, $CHCl_3$ CD: 25°, EtOH. IR: KBr. ^1H NMR: (200 MHz or 600 MHz) and ^{13}C NMR (150.9 MHz) were recorded in $CDCl_3$ with the solvent as int. standard ($CDCl_3$, δ 7.26 and δ 77.01, resp.). Proton detected, heteronuclear correlations were measured using HMQC (Heteronuclear Multiple Quantum Correlation, optimized for $^1J_{HC} = 150$ Hz) and HMBC (optimized for $^nJ_{HC} = 7$ Hz). EIMS: 70 eV. TLC: precoated silica gel 60 F_{254} plates (Merck), deactivated with NH_3. Spots were visualized under UV light and by Dragendorff's reagent. Prep. TLC: plates with a layer thickness of 2 mm and a concn zone (Merck) were used; 80–100 mg samples were applied and recovered with 25% MeOH in $CHCl_3$ after resolution. HPLC (analytical): Novapak C_{18} (4 μm, 3.9 mm × 150 mm, Waters), flow 1 ml min^{-1}; HPLC (prep.): Novapak C_{18} (6 μm, 7.8 mm × 200 mm, Waters), flow 4 ml min^{-1}, UV detection 200–400 nm (photodiode array detector). HSCCC: $CHCl_3$–MeOH–0.1 M HCl (5:5:3), mobile phase: lower phase, (H) → T, Triple Coil No. 14, 1.7 mm × 950 mm (large coil), TLC detection (see above), flow 2 ml min^{-1}, 850 min^{-1}.

Plant material. Stems and leaves of *A. robertsoniorum* Léonard were collected in November 1992 in the Buda Mafisini Forest in Kenya and identified by one of us (R.H.). A voucher specimen is deposited at the Nairobi National Museums' Herbarium.

Extraction and isolation. Air-dried stems (0.5 kg) were ground and extracted exhaustively with 1'N H_2SO_4–MeOH (5:1). After evapn of MeOH, the aq. soln was extracted with *n*-hexane, $CHCl_3$ and, after basification with conc. NH_3 soln (pH 8), with *n*-BuOH. ^1H NMR and the Dragendorff test proved the $CHCl_3$ fr. to be the only alkaloid-containing fr. After evapn of solvent, the residue (*ca* 5 g) was subjected to HSCCC (1 g per run). Portions of 4 ml were collected, monitored by TLC and then combined. In the following, the alkaloids are described according to their polarity and, thus, order of isolation.

Isolation of ancistrobertsonine A (**2**). Fr. 3 obtained from the HSCCC sepn was further resolved by prep. TLC using $CHCl_3$–MeOH (19:1) as eluent. The least polar fr. gave 61 mg of **2** as a microcrystalline powder from MeOH–H_2O. Mp 220–222°. $[\alpha]_D^{25}$ +29° ($CHCl_3$; *c* 0.53). CD: $\Delta\varepsilon_{212}$ −68.2, $\Delta\varepsilon_{218}$ −51.9, $\Delta\varepsilon_{224}$ −66.8, $\Delta\varepsilon_{238}$ +108.8 (EtOH, *c* 0.02). IR ν_{max} cm^{-1}: 3380 (O–H), 2980, 2930, 2910 (C—H), 1600, 1585, 1575 (C=C), 1260 (C–O). ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (3H, *d*, $J = 5.4$ Hz, Me-3), 1.56 (3H, *d*, $J = 6.3$ Hz, Me-1), 1.94 (1H, *dd*, $J_{eq} = 6.4$ Hz, $J_{gem} = 16.6$ Hz, H_{eq}-4), 2.34 (3H, *s*, Me-2'), 2.43 (1H, *dd*, $J_{gem} = 16.6$ Hz, H_{ax}-4, J_{ax} not measurable due to partial peak overlap by signal of *N*-Me), 2.46 (1H, m_c, H-3), 2.54 (3H, *s*, *N*-Me), 3.87 (3H, *s*, OMe-8), 3.90 (1H, *q*, $J = 6.3$ Hz, H-1), 3.94 (3H, *s*, OMe-4'), 3.98 (3H, *s*, OMe-5'), 6.53 (1H, *s*, H-7), 6.67 (1H, *s*, H-3'), 6.72 (1H, *s*, H-1'), 6.84 (1H, *d*, $J = 8.0$ Hz, H-6'), 7.26 (1H, *d*, $J = 8.0$ Hz, H-7'). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 18.7 (Me-3), 20.3 (Me-1), 22.0 (Me-2'), 29.5 (C-4), 34.7 (C-3), 41.1 (*N*-Me), 55.3 (OMe-8), 56.2 (OMe-4'), 56.4 (OMe-5'), 56.0 (C-1), 97.0 (C-7), 105.3 (C-6'), 108.9 (C-1'), 116.1 (C-10'), 116.3 (C-3'), 117.3 (C-5), 121.7 (C-8'), 131.0 (C-7'), 131.1 (C-10), 134.5 (C-9), 135.9 (C-9'), 137.5 (C-2'), 153.6 (C-6), 156.3 (C-8), 157.5 (C-4'), 157.9 (C-5'). EIMS: *m/z* (rel. int.): 421 $[M]^+$ (1), 406 $[M-Me]^+$ (100). HRMS *m/z* 406.202 $[M-Me]^+$ ($C_{25}H_{28}NO_4$ requires: 406.202).

Isolation of ancistrobrevine B (**4**). The major alkaloid of HSCCC fr. 4 was isolated by prep. TLC, as described above for **2**. By recrystallization from MeOH–H_2O, 55 mg of **4** were obtained as a fine powder. Mp 150–151°; ref. [19]: mp 122–124°; ref. [13]: mp 122–124°. $[\alpha]_D^{25}$ +84° ($CHCl_3$; *c* 0.13); ref [19]: $[\alpha]_D^{25}$ +68° ($CHCl_3$; *c* 0.82).* ^1H NMR, MS and CD data identical to an authentic sample prepd earlier [13, 19]. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 20.5 (Me-3), 22.1 (Me-1), 22.1 (Me-2'), 33.9 (C-4), 42.8 (C-3), 47.6 (C-1), 55.2 (OMe-8'), 56.3 (OMe-4'), 56.5 (OMe-5'), 96.3 (C-7), 105.3 (C-6'), 109.0 (C-3'), 116.2 (C-10'), 116.8 (C-5), 116.9 (C-1'), 122.6 (C-8'), 129.7 (C-7'), 134.8 (C-9), 136.1 (C-9'), 136.8 (C-10), 137.4 (C-2'), 152.5 (C-6), 156.6 (C-8), 157.5 (C-4'), 157.7 (C-5'). The assignment of C-5 and C-10' may be interchangeable, because of overlapping correlations in the HMBC spectrum.

Isolation of ancistrocladine (**3a**) *and hamatine* (**3b**). From fr. 5, ancistrocladine (**3a**) and hamatine (**3b**) were isolated by HPLC, analytically with MeOH–H_2O (1:1), preparatively with MeOH–H_2O (4:6) 24 min, (4:6 → 7:3) in 1 min, (7:3) 14 min, (7:3 → 4:6) in 1 min, (4:6) 20 min. In this way, 41 mg of fr. 5 were resolved to yield 13 mg of ancistrocladine (**3a**) and 28 mg of hamatine (**3b**), which were separately recrystallized from MeOH–H_2O to give 8 mg of pure **3a** and 24 mg of pure **3b**. Ancistrocladine (**3a**). Mp 261–263°; ref. [13]: mp 260–263°. $[\alpha]_D^{25}$ −21° ($CHCl_3$, *c* 0.07); ref. [13]: $[\alpha]_D^{25}$ −20° ($CHCl_3$, *c* 0.15). IR, chiroptical ^1H NMR and MS data identical to those from samples prepd earlier [13, 17–19]. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 18.5 (Me-3), 18.6 (Me-1), 20.0 (Me-2'), 31.9 (C-4), 44.1 (C-3), 47.8 (C-1), 55.5 (OMe-8'), 56.4 (OMe-4'), 56.6 (OMe-5'), 97.1 (C-7), 106.1 (C-6'), 109.1 (C-3'), 115.0 (C-10'), 116.0 (C-5), 116.8 (C-1'), 119.7 (C-8'), 127.8 (C-7'), 131.8 (C-9), 133.9 (C-9'), 136.6 (C-10), 138.9 (C-2'), 153.6 (C-6), 156.6 (C-8), 157.7 (C-4'), 157.9 (C-5'). Hamatine (**3b**). Micro-

* The sign of the optical rotation in ref. [13]: $[\alpha]_D^{25}$ −68° is a misprint [5]. For correct data see ref. [19]: $[\alpha]_D^{25}$ +68°.

crystalline powder. Mp 240–242°; ref. [20]: mp 250–252°; ref. [13]: mp 247–248°. $[\alpha]_D^{25}$ +16° ($CHCl_3$, *c* 0.32); ref. [20]: $[\alpha]_D^{25}$ +77° ($CHCl_3$, *c* 0.86); ref. [13]: $[\alpha]_D^{25}$ +64° ($CHCl_3$, *c* 0.24). IR, chiroptical ^1H NMR and MS data identical to those from former isolation [13] and synthetic work [17, 18]. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 18.5 (Me-1), 18.6 (Me-3), 20.5 (Me-2′), 31.8 (C-4), 44.1 (C-3), 47.6 (C-1), 55.5 (8-OMe), 56.4 (5′-OMe), 56.5 (4′-OMe), 97.2 (C-7), 106.6 (C-6′), 108.6 (C-3′), 114.9 (C-9′), 116.3 (C-5), 116.7 (C-10′), 117.6 (C-8′), 120.3 (C-1′), 128.2 (C-7′), 131.6 (C-10), 136.8 (C-9′), 137.1 (C-2′), 153.8 (C-6), 156.6 (C-8), 157.5 (C-4′), 157.8 (C-5′). The assignment of Me-1 and Me-3 may be interchangeable, because of overlapping correlations in the HMQC spectrum

Oxidative degradation of **2** *and* **4**. The degradation, the derivatization of the amino acids and the subsequent GC-MSD analysis were carried out as described recently [14, 15].

Acknowledgements—We wish to thank Dr. D. Koppler and M. Rückert for performing the HMQC and HMBC experiments. This work was supported by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 'Magnetische Kernresonanz *in vitro* und *in vivo* für die biologische und medizinische Grundlagenforschung' and SFB 251 'Ökologie, Physiologie und Biochemie pflanzlicher und tierischer Leistung unter Streß and Normalverfahren) and by the Fonds der Chemischen Industrie.

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