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Cyclopeptide alkaloids from *Heisteria nitida*

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Abstract

Integerrenine, and a new cyclopeptide alkaloid, containing the unusual amine oxide function, anorldianine 27-N oxide, stigmasterol, β-sitosterol, lupeol, (+)-catechin, (—)-epicatechin and 4-hydroxy-2-methoxy benzoic acid were isolated from the Ecuadorian medicinal plant *Heisteria nitida* (Engl.), Olacaceae. The structures were determined by UV, IR, NMR and mass spectroscopic investigations and chemical transformations. The cyclopeptide alkaloids have been isolated and characterized for the first time in the family Olacaceae. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Heisteria nitida*; Olacaceae; Cyclopeptide alkaloids; Anorldianine 27-N oxide; Integerrenine

1. Introduction

Heisteria (Jacq.), Olacaceae, is a genus of small trees primarily found in tropical America and West Africa. *H. nitida* has been used in traditional medicine for treatment of diarrhoea and hepatic infection (Ghia, F., *Personal communication*, 1992). Various *Heisteria* species are used by South-American Indians in the treatment of rheumatism, abscesses, headache, throat infections, swellings, nose bleedings, pain in joints and muscles (Kvist & Holm-Nielsen, 1987; Pinkley, 1969; Russo, 1992; Schultes & Raffauf, 1990; Sleumer, 1984; Williams, 1936). *H. pallida* is reported to have anti-phlogistic effect after external application in patients with rheumatism and arthritis (Wiemann, 1990). Two varieties of *H. accuminata* have been investigated in the rat-paw oedema model where one of the extracts showed a moderate inhibition of carrageenan induced oedema (Ortega, Carretero, Pascual, Villar & Chiriboga, 1996). Scopolamine have been isolated from *H. olivae* (Cairo Valera, De Budowski, Delle Monache & Marini-Bettolo, 1977). Triterpenes and proanthocyanidines have been isolated from *H. pallida* (Gonzalez, Gonzalez, Ferro & Ravelo, 1988; Dirsch, Wiemann & Wagner, 1992; Dirsch, Neszmèlyi & Wagner, 1993). Recently from *H. accuminata* several acetylenic fatty acids have been isolated and structurally determined (Kraus, Neszmèlyi, Holly, Wiedemann, Nenninger, Torssell et al., 1998). *H. nitida* (Engl.) has not been investigated previously. The aim of this study was to find novel chemical structures with anti-inflammatory or anti-viral activity. Preliminary pharmacological tests of crude extracts from the bark of *H. nitida* showed moderate or weak anti-inflammatory (PAF, PG tests), anti-viral activity and toxic properties. However, the NMR spectra showed interesting features which directed the study to isolation and characterization of new chemical structures.

Cyclopeptide alkaloids are widespread and occur in several families: Asteraceae, Celastraceae, Euphorbiaceae, Menispermaceae, Pandaceae, Rhamnaceae, Rubiaceae, Sterculiaceae and Urticaceae (Gournelis, Lascaris & Verpoorte, 1997). Anti-fungal, antibacterial and sedative activities of cyclopeptide

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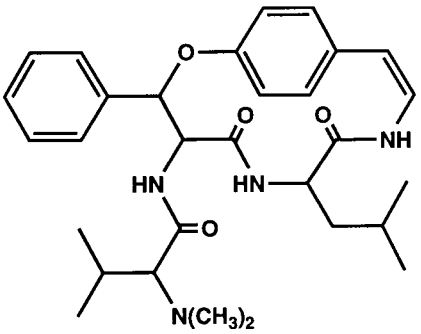

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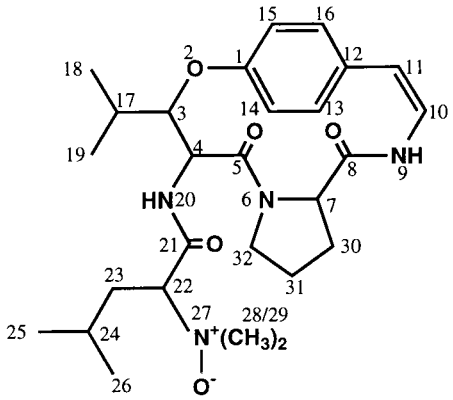

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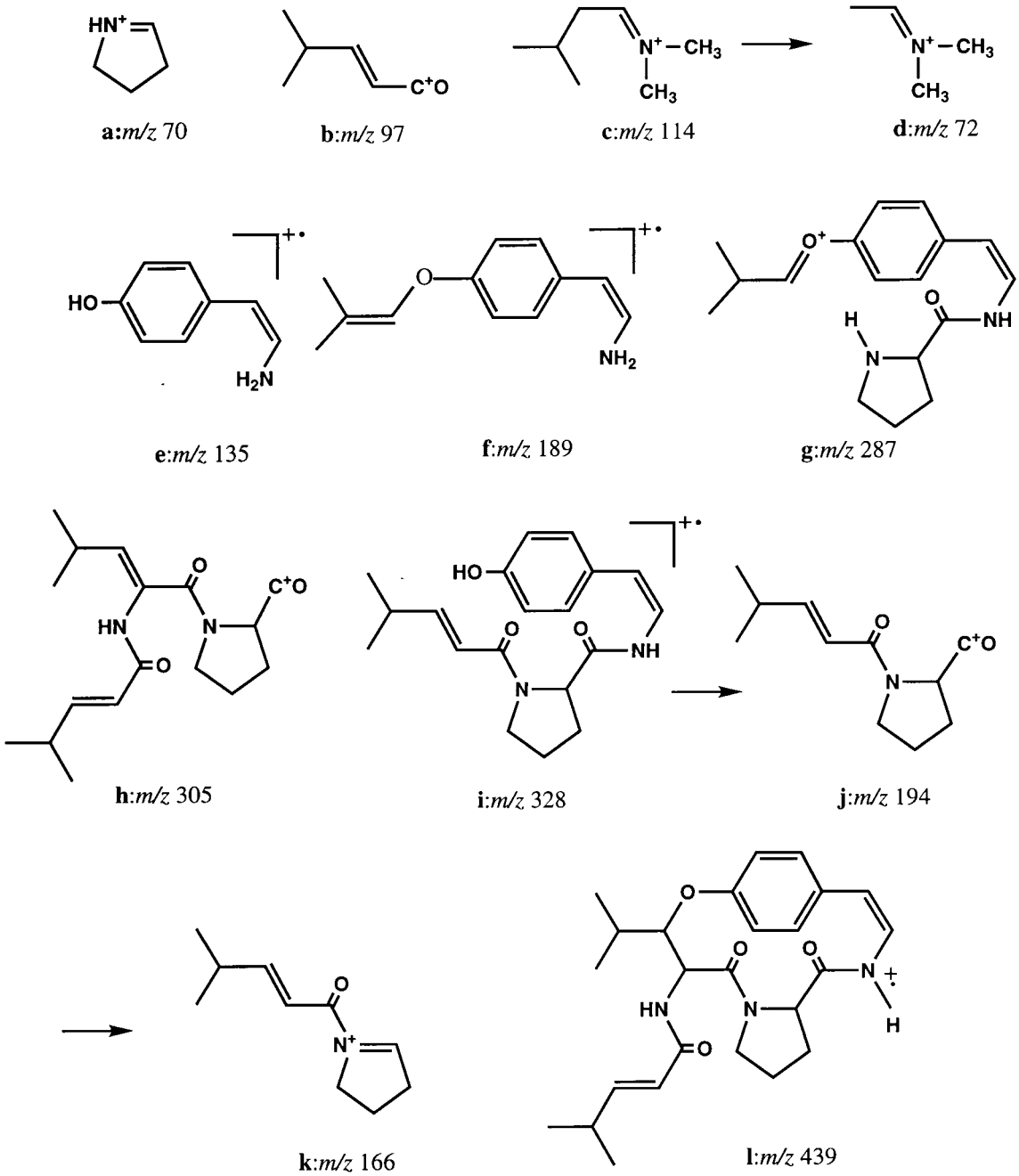
alkaloids have been reported (Gournelis et al., 1997; Tschesche, David, Serbes, Von Radloff, Kaussmann & Eckhardt, 1974; Schmidt, Lieberknecht & Haslinger, 1985; Pandey & Devi, 1990; Blanpin, Païs & Quevauviller, 1963). In the present work cyclopeptide alkaloids have been isolated and characterized for the first time in the family Olacaceae.

2. Results and discussion

The ^{1}H NMR spectrum of the crude ethyl acetate extract showed some interesting features both in the aromatic, olefinic and aliphatic methyl regions. From the unpolar fractions long chain hydrocarbons, fatty acids and fatty acid methyl esters, stigmasterol, β-sitosterol and lupeol were isolated. From the most polar

Table 1
^{1}H and ^{13}C NMR correlation data of **2**; At 400 MHz (^{1}H) and 100.6 MHz (^{13}C), in $CDCl_3$ with TMS as int. standard. Chemical shifts are relative to residual $CHCl_3$ for ^{1}H (*d* 7.25) and to the solvent for ^{13}C (δ 77.00). The multiplicity of the carbons was assigned from the HMQC and DEPT spectra

Position	Kind of carbon	^{13}C shift δ_C	^{1}H shift δ_H (multi., J_{HH} Hz)	HMBC correlations via $^{2,3}J_{CH}$
1	*q*C═	157.5 (*s*)	–	H-3
3	CH	83.4 (*d*)	5.01 (*dd*, 8.2; 1.5)	H-18; H-19; H-17
4	CH	53.9 (*d*)	4.78 (*br* $w_{1/2}$ 18 Hz)	–
5	C═O	170.9 (*s*)	–	H-3; H-7
7	CH	62.9 (*d*)	4.21 (*d*, 8.2)	H-30; H-31
8	C═O	167.1 (*s*)	–	H-7; NH-9; H_α-30; H_β-30
9	NH	–	6.20 (*d*, 10.2)	–
10	CH═	126.4 (*d*)	6.64 (*dd*, 10.2; 7.3)	NH-9; H-11
11	CH═	116.3 (*d*)	6.39 (*d*, 7.3)	H-10; NH-9
12	qC═	131.7 (*s*)	–	H-11; H-10
13	CH═	130.6 (*d*)	6.96 (*d*, 7.3)	–
14	CH═	120.7 (*d*)	7.07 (*d*, 7.3)	–
15	CH═	121.1 (*d*)	7.29 (*d*, 8.8)	–
16	CH═	132.1 (*d*)	7.10 (*d*, 8.8)	–
17	CH	29.0 (*d*)	1.26 (*m*)	H-18; H-19; H-3
18	CH_3	15.2 (*q*)	0.99 (*d*, 6.7)	H-19
19	CH_3	20.6 (*q*)	1.24 (*d*, 6.7)	H-3
20	NH	–	9.64 (*br s*)	–
21	C═O	165.9 (*s*)	–	–
22	CH	77.2 (*d*)	4.64 (*br d*, 10.3)	H-28; H-29
23	CH_2	36.3 (*t*)	1.70 (*m*), 1.98 (*m*)	H-25; H-26
24	CH	25.7 (*d*)	1.25 (*m*)	H-25; H-26
25	CH_3	21.4 (*q*)	0.94 (*d*, 6.4)	H-26
26	CH_3	23.9 (*q*)	0.93 (*d*, 6.4)	–
28	$N(CH_3)$	54.2 (*q*)	3.35 (*s*)	H-29
29	$N(CH_3)$	55.1 (*q*)	3.40 (*s*)	H-28
30	CH_2	28.2 (*t*)	1.47 (*m*), 2.32 (*m*)	H-7
31	CH_2	23.9 (*t*)	1.70 (*m*), 1.90 (*m*)	H-7
32	CH_2	46.9 (*t*)	3.35 (*m*), 3.86 (*m*)	H-7



Scheme 1. Most significant mass spectral fragments of compound **2**.

fractions two cyclopeptide alkaloids: integerrenine **1** and a new alkaloid, anorldianine 27-N oxide **2**, belonging to the same type of tetrameric cyclopeptides were obtained.

The high resolution mass spectrum of the major alkaloid **1** (Scheme 1) in the FAB (positive) mode gave an $[M+H]^+$ ion at m/z 535.3286 corresponding to a molecular formula of $C_{31}H_{42}N_4O_4$. Our UV, IR, ^1H and EI MS spectra of the compound agreed well with previously published data for the cyclopeptide alkaloid integerrenine (Tschesche, Rheingans, Fehlhaber & Legler, 1967; Medina & Spiteller, 1981; Lagarias, Goff, Klein & Rapoport, 1979). It ought to be observed that the ^1H and ^{13}C NMR spectra are different in pure $CDCl_3$ and in $CDCl_3$-10% CD_3OD as a result of conformational changes of the molecule in different solvents (Haslinger, 1978).

The new peptide alkaloid, m/z $[M+H]^+$ 501, corre-

sponding to the elementary composition $C_{27}H_{40}N_4O_5$, was isolated as a semisolid from a more polar fraction. It gave a slightly yellow colour with Dragendorff's reagent. The IR spectrum exhibited absorption bands for —NH—CO, C═C and Ar—O—C groups. The UV spectrum showed absorption maxima at 320 and 266 nm typical for a styrylamine chromophore in cyclopeptide alkaloids (Tschesche, David, Uhlendorf & Fehlhaber, 1972). The ^1H, ^{13}C NMR, DEPT and HMQC spectra showed the presence of a 14-membered cyclic system consisting of the three amino acids leucine, proline and 3-hydroxyleucine, three carbonyl groups at δ_C 170.9, 167.1 and 165.9 ppm. The olefinic carbon atoms were located at δ_C 116.3 and 126.4 ppm and a *p*-hydroxystyryl amine unit which derives from tyrosine by degradation. In the HMBC spectrum the signal at δ_C 167.1 showed two-bond ^1H-^{13}C correlations with δ_H 6.20 of the styrylamino NH-9 and δ_H 4.21 of the proton H-7 of proline. Moreover three-bond correlations to β and β′ protons of the amino acid at δ_H 1.47 and 2.32, were also present. For the signal at δ_C 170.9, three-bond correlation peaks to H-7 (δ_H 4.21) and H-3 (δ_H 5.01) were found. More HMBC data are summarized in Table 1. The methyl absorptions at δ 3.35 and 3.40 ppm were puzzling because with reference to the elementary composition it was not possible to accomodate two methoxy groups in the molecule and the N—CH_3 absorptions normally occur in the δ 2.0–2.5 ppm region. Another possibility was that the compound contained the unusual amine oxide function O^-—$N^+(CH_3)_2$ with two prochiral N-methyl groups (C-28, 29), δ_H 3.35 and 3.40 ppm, δ_C 54.2 and 55.1 ppm ($CDCl_3$, 10% CD_3OD). Before we realized that the compound contained this polar amine oxide function we experienced considerable loss of substance by trying to purify the compound on preparative silica gel plates. However, column chromatography on Sephadex LH-20 was successful. The shifts of the C-3, δ 83.4 ppm, C-4, δ 53.9 ppm, and $J_{3,4\text{-H}} = 8$ Hz indicated an L-erythro-3-hydroxyleucine structural unit (Gournelis et al., 1997). The vicinal coupling constant of 3,17-H was small, approximately 1–1.5 Hz and the four C—CH_3 groups appeared as doublets at δ 1.24, 0.99, 0.94 and 0.93 ppm. Four methylene groups were observed in the DEPT spectrum, in agreement with the incorporation of one proline and one leucine unit. Hydrolytic cleavage of the alkaloid gave free proline. The studies of the fragmentation pattern in the EI and FAB MS spectra gave conclusive evidence for the structure. Scheme 1 shows the prominent fragments, the formation of which follows earlier proposed fragmentation scheme (Tschesche & Kaussmann, 1975). Of interest is the peak **l** at m/z = 439, which corresponds to the expected Cope reaction product, M^+ minus [$(CH_3)_2$ NOH]. The ion **e** at m/z 135 revealed the presence of a styrylamine unit, the ion **f** at m/z 189 indicated a 3-hydroxylated leucine unit and the odd-electron ion **i** at m/z 328 and its fragmentation ions **j** and **k** proved that proline was part of the molecule. All together, the data fit the structure **2** for the alkaloid. The deoxy compound anorldianine has previously been isolated from *Canthium anorldianum* (Dongo, Ayafor, Sondengam & Connolly, 1989).

3. Experimental

3.1. General

The ^1H, ^{13}C NMR, HMQC (heteronuclear multiple quantum correlation) and HMBC (heteronuclear multiple bond correlation) spectra were recorded at 400/100.6 MHz in $CDCl_3$ on a Bruker DRX 400 instrument with TMS as internal standard. The IR spectra were recorded with a Nicolet MX-S, the UV spectra with a Perkin-Elmer Lambda 2UV/VIS spectrophotometer and the EI MS and positive-ion FAB MS (with glycerol as matrix) spectra were recorded with a JEOL JMS SX/SX102A instrument (JEOL, Japan). The melting points were determined using a Digital Melting Point Apparatus (model IA 8103, Electrothermal Engineering Ltd, Southend-on-Sea, Essex, UK) and are uncorrected. Optical rotation was determined at ambient temperature using a Perkin-Elmer polarimeter 241. TLC was performed on precoated aluminum sheets on silica 60 F_{254}, 0.25 mm (Merck, Darmstadt, Germany) and preparative TLC was performed on silica gel (60, $PF_{254+360}$, Merck) glass plates, 20 × 20, 0.25 and 0.5 mm (Merck). UV light (245 and 366 mm) and spraying with vanillin-sulfuric acid reagent followed by heating (120°), was used for detection.

Medium-pressure liquid chromatography (MPLC) was performed using a SEPARO AB MPLC equipment (Baeckström Separo AB, Lidingö, Sweden) (Jirón, 1996). SEPARO Variable length glass columns with an inner diameter of 1.5 or 2.5 cm, packed with silica gel 60, 40–63 μm (Merck) were used. A FMI Lab pump, model QD (Fluid Metering Inc., Oyster Bay, NY, USA) was used at a flow rate of 20–30 ml/min. Fractions of 9 ml were collected with a Gilson fraction collector model 201. The columns were eluted with continuous gradients running from hexane, over CH_2Cl_2 to MeOH, and H_2O afforded by a SEPARO constant-volume mixing chamber combined with an open reservoir. Initially, the mixing chamber contained 50 ml non-polar solvent and the reservoir the first of 15–20 premixed binary (less polar/more polar solvent) gradient mixtures, of 20–40 ml each, which were successively fed to the reservoir during the separation.

3.2. Plant material

The bark of *Heisteria nitida* (Engl.), was collected by Dr Felipe Ghia in 1992 at the Reserva Biologica, Jatun Sacha, Provincia del Napo, Ecuador. Voucher specimens are deposited in the Herbario Economico, Escuela Politecnica Nacional, EPN, Quito, Ecuador, (G. F. 539) and in the Herbarium of the Department of Systematic Botany, Uppsala University, Sweden.

3.3. Extraction

The plant material was dried at 40° in the dark in a ventilated hood and grounded. The material, 1.1 kg, was extracted exhaustively at room temperature three times with light petroleum (40–60°) with occasional stirring followed by three times with methanol for 8 days each time. The extracts were evaporated in vacuo to give 8.3 and 86.5 g of a gelatinous and an oily material respectively. The methanol extract was partitioned between ethyl acetate and water to give 17.2 g of an ethyl acetate soluble fraction. An insoluble residue (2.8 g) was discarded. The water phase was freeze dried to give 66.6 g of crude material which consisted mainly of carbohydrates. It was not further investigated.

3.4. Isolation and purification

The ethyl acetate fraction, 16 g, was subjected to SEPARO column chromatography on silica gel 60 (30 g) with gradient elution using hexane-CH_2Cl_2 and EtOAc-MeOH. At low solvent polarity stigmasterol, β-sitosterol and lupeol were eluted as identified by ^{1}H NMR spectroscopy. The CH_2Cl_2-EtOAc fractions contained impure integerrenine **1** mixed with fatty acid material. Increased polarity gave small amounts of impure anorldianine 27-N oxide **2**. It was purified by chromatography on a Sephadex LH-20 column using gradient elution with $CHCl_3$–MeOH, and EtOAc–MeOH mixtures. At still higher eluent polarity (+)-catechin, (−)-epicatechin and 4-hydroxy-3-methoxybenzoic acid were obtained.

Stigmasterol was purified by chromatography on prep. TLC plates using $CHCl_3$–MeOH (99:1) as eluent, 63 mg. It was identified by its ^{1}H NMR spectrum.

β-Sitosterol was purified by chromatography on prep. TLC plates using $CHCl_3$–MeOH (98:2) as eluent, 87 mg. It was identified by its ^{1}H NMR spectrum.

Lupeol was purified by chromatography on prep. TLC plates using $CHCl_3$–MeOH (95:5) as eluent, amorphous solid, 57 mg, $[\alpha]_D^{22}$ +27.3° ($CHCl_3$; *c* 0.4). ^{1}H and ^{13}C NMR data agreed with lit. data (Connolly & Hill, 1991).

Integerrenine **1** was purified by chromatography on a Sephadex LH-20 column using CH_2Cl_2 as eluent. Further purification was achieved by dissolving the combined fractions containing integerrenine in 0.1 N hydrochloric acid, basification with solid $NaHCO_3$ and extraction with chloroform followed by prep. TLC using $CHCl_3$–MeOH (99:1) as eluent, 240 mg, mp 278° (acetonitrile), lit. [21] mp 274°, $[\alpha]_D^{22}$ −232°C ($CHCl_3$; *c* 0.2) HRFAB-MS, found: *m/z* $[M+H]^+$, 535.3286. Cal. for $[M+H]^+$ $C_{31}H_{43}$ N_4 O_4, 535.3284; EI-MS and the ^{1}H NMR data agreed with published data of integerrenine (Tschesche et al., 1967; Medina & Spiteller, 1981; Lagarias et al., 1979).

Anorldianine 27-N oxide **2** was purified by chromatography on a Sephadex LH-20 column using CH_2Cl_2–MeOH (1:1) as eluent. Further purification was achieved by dissolving the combined fractions containing **2a** in 0.1 N hydrochloric acid, basification with solid $NaHCO_3$ and extraction with chloroform. The yield of **2a** was 45 mg. IRν_{max}^{KBr} cm^{-1} 3343, 1675 (secondary amide), 2790 (N—Me), 1623 (conjugated C=C), 1241, 1115 (aryl ether). UVλ_{max}^{MeOH} (log ϵ): 266 (3.71), 320 (3.31). HRFAB-MS, found: $[M+H]^+$, 501.3062, $C_{27}H_{41}$ N_4 O_5 requires $[M+H]^+$, 501.3072; EI-MS *m/z* (rel. int.): 500 $[M]^+$ (<1), 439 (76), 328 (25), 305 (78), 287 (8), 251 (19), 214 (19), 194 (30), 189 (100), 166 (18), 135 (23), 114 (37), 97 (70), 89 (37), 70 (99), 61 (60), 60 (71), 42 (74). The ^{1}H and ^{13}C NMR data are listed in Table 1.

Hydrolysis of anorldianine 27-N oxide **2a** (ca 200 μg) was hydrolyzed with 6 M HCl (100 μl, 100°, 16 h) in a sealed glass tube. After evaporization, esterification was performed with 100 μl of 1 M methanolic HCl (100°, 30 min). For N-acetylation, MeOH–Ac_2O (4:1) was added to the methyl ester in 100 μl H_2O at room temp. (45 min). The product in MeOH was analyzed by GC-MS using an HP-5, 25 m fused silica WCOT column, temp. programmed 140° for 3 min–230° for 6 min, the MS of the peak at ret. time 8.2 min was identical to an authentic sample of N-acetylproline methyl ester.

(+)-Catechin was purified by chromatography on a Sephadex LH-20 column using $CHCl_3$–MeOH (1:9) as eluent, amorphous solid, 46 mg, $[\alpha]_D^{22}$ +11.3° (Me_2CO; *c* 0.2). The ^{1}H and ^{13}C NMR data agreed with lit. data (Morimoto, Nonaka, Nishioka, Ezaki & Takizawa, 1985; Baldé et al., 1991).

(—)-Epicatechin was purified by chromatography on a Sephadex LH-20 column using MeOH as eluent, amorphous solid, 35 mg, $[\alpha]_D^{22}$ −12.2° (Me_2CO; *c* 0.2). The ^{1}H and ^{13}C NMR data agreed with lit. data (Morimoto et al., 1985; Baldé et al., 1991).

4-Hydroxy-2-methoxybenzoic acid, was purified by chromatography on Sephadex LH-20 using MeOH as eluent followed by prep. TLC using $CHCl_3$–MeOH–H_2O (3 : 9 : 1) as eluent, 28 mg. It was identified by its ^{1}H NMR spectrum.

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