A New Benzochromanone Derivative from Cape Aloe†

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A new compound was isolated from a commercial sample of Cape aloe, and its structure was determined by spectral analysis. This benzo[*f*]chroman-3-one (**1**) occurs in the drug in racemic form. The synthesis of an analogous chromanone (**9**) via intramolecular thermal acid-catalyzed cyclization of the 2-naphthyl cinnamate (**11**) strongly supports the formation of **1** as a process product.

Keywords: *Cape aloe; process product; benzo[f]chroman-3-ones; polyketides; p-coumaric acid*

INTRODUCTION

Characterization of process products is a matter of growing interest because of the well-recognized influence of these molecules on nutritional value, flavor, and safety of foods (Walker and Quattrucci, 1988).

Aloe, which is the dried exudate from the cut leaves of plants of *Aloe* spp. (Tyler et al., 1988), is potentially rich in products arising from thermal treatments. In fact, the commercial drug, currently used for its bittering and cathartic properties (Council of Europe, 1981), results from prolonged heating and storage of the fresh leaf juice (Trease and Evans, 1983). Recently, from a commercial sample of Cape aloe, we isolated a 1,1-diphenylethane derivative that can be considered the first process product found in the drug (Speranza et al., 1994). In a continuation of this work, we describe here the isolation and chemical characterization of a new process product that has a benzochromanone nucleus. We also suggest a hypothetical route for the formation of this product in the drug.

MATERIALS AND METHODS

Drug Samples. The commercial Cape aloe used in this investigation was purchased from Meihwizen Exporters Pty Ltd. and was produced in the Port Elizabeth region (Cape Town, South Africa).

General Methods. IR and UV spectra were recorded on a Jasco IR 5000 instrument (Japan Spectroscopic Company, Tokyo) and a Hewlett-Packard (model 845217A) diode array spectrophotometer (Hewlett-Packard Gmbh, Waldbronn, Germany), respectively. Fast-atom bombardment (FAB) and electron-impact (EI) mass spectra were obtained on a VG 7070 EQ mass spectrometer (VG Instruments, Manchester, U.K.): ionization energy was 70 eV, and the matrix for FAB MS was glycerol. The ^{1}H and ^{13}C NMR spectra were measured with a Bruker AC 300 spectrometer equipped with an ASPECT 3000 computer operating at a basic frequency of 300 MHz, using the solvent as internal standard ($CDCl_3$ at 7.25 and 77.00 ppm, CD_3OD at 3.30 and 49.00 ppm, DMSO-d_6 at 2.50 and 39.5 ppm). Analytical HPLC and droplet counter current chromatography (DCCC) systems, as well as experimental contitions for TLC and flash chromatography have been reported previously (Speranza et al., 1994).

Isolation of Compound CA-14 (1). Cape aloe (2 kg of powdered drug) was extracted and processed as previously described (Speranza et al., 1994). After two succesive flash chromatographies and a DCCC separation carried out as reported and monitored by TLC (eluent $CHCl_3$:ethyl acetate: acetic acid, 10:3:1), 340 mg of a residue enriched in compound CA-14 (R_f, 0.58) was obtained. Further flash chromatography over silica gel (eluent, $CHCl_3$:ethyl acetate, 2:1) afforded **1** (98 mg) as an amorphous solid that was shown to be pure by TLC and analytical HPLC (column: LiChrospher100 RP-18, 5 μm, 125 × 4 mm, Merck; flow rate, 1 mL/min; UV detection at λ 254 nm; mobile phase, CH_3CN:H_2O; linear gradient from 30 to 60% CH_3CN in 15 min; R_t, 8.1 min); mp: 272−274 °C (uncorrected); IR (KBr) 3316, 1748, 1667, 1620, 1582, 1514 cm^{-1}; UV (CH_3OH) λ_{max} 228 (log ϵ 4.61), 256 (4.52), 310 (3.75), 340 nm (3.45); ^{1}H and ^{13}C NMR: see Table 1; EI-MS *m/z* 378 (M^+), 363, 350, 335; FAB MS 377 $(M-H)^-$; HR EI-MS 378.1104000 (M^+, calcd for $C_{22}H_{18}O_6$: 378.1103386).

Methylation of Compound CA-14 (1). A mixture of compound CA-14 (20 mg), dimethyl sulfate (0.15 mL), and anhydrous K_2CO_3 (400 mg) in dry acetone (3 mL) was refluxed with stirring under N_2 for 2.5 h. After cooling, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried over Na_2SO_4, evaporated, and purified by flash chromatography (eluent $CHCl_3$:hexane, 6:1) to give the trimethyl ether **2** (18.6 mg) that was shown to be pure by TLC analysis (eluent $CHCl_3$:hexane, 6:1, R_f, 0.43): IR (KBr) 1781, 1707, 1613, 1582, and 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H, CH_3-Ar), 2.68 (s, 3H, CH_3CO), 3.06 (dd, J = 15.4, 2.0 Hz, 1H, H-2a), 3.17 (dd, J = 15.4, 7.3 Hz, 1H, H-2b), 3.70 (s, 3H, 9-OCH_3), 3.73 (s, 3H, 4′-OCH_3), 3.93 (s, 3H, 6-OCH_3), 4.64 (dd, J = 7.3, 2.0 Hz, 1H, H-1), 6.57 (s, 1H, H-5), 6.78 (d, J = 8.6 Hz, 2H, H-3′, H-5'), 6.81 (s, 1H, H-10), 7.02 (d, J = 8.6 Hz, 2H, H-2′, H-6′); ^{13}C NMR ($CDCl_3$) δ 20.44 (CH_3-Ar), 32.63 (CH_3CO), 37.47 (C-1), 37.97 (C-2), 55.18 and 55.53 (3 × OCH_3), 97.75 (C-5), 99.83 (C-10), 108.96 (C-10b), 114.55 (C-3′, C-5′), 117.91 (C-6a), 127.86 (C-2′, C-6′), 132.61, 132.89, 133.21 and 134.29 (C-1′, C-7, C-8, C-10a), 150.63, 154.41, 158.84 and 159.84 (C-4a, C-6, C-9 and C-4′), 167.16 (C-3), 206.37 (CH_3CO); EI-MS *m/z* 420 (M^+), 405, 378, 241.

Resolution of Compound CA-14 into Its Enantiomers. Separation of the enantiomers of racemic **1** was carried out by reversed-phase HPLC with the following chromatographic conditions: column, 4.6 × 250 mm β-cyclodextrin (= Daltosil 100, 4 μm; Serva, Heidelberg, Germany); eluent, CH_3OH:H_2O (1:1); flow rate, 0.8 mL/min; temperature, 25 °C; detector, UV λ 254 nm. The 1:1 ratio of enantiomers (R_t, 20.62 and 23.57 min) was determined by measuring the peak areas.

Synthesis of 6-Hydroxy-1-(4-methoxyphenyl)benzo[*f*]-chroman-3-one (9). To a suspension of 1,3-dihydroxynaphthalene (**7**; 160 mg, 1 mmol) and *p*-methoxycinnamic acid (**8**; 178 mg, 1 mmol) in dry toluene (6 mL), 3 mL of freshly prepared polyphosphoric acid (PPA; Dupin and Chenault, 1983) was added, and the reaction mixture was heated at 90 °C for 1 h under N_2 with stirring. After cooling, the mixture was poured into crushed ice and extracted with ethyl ether (2 × 50 mL). The organic layer was washed with water and with a saturated $NaHCO_3$ solution, and dried over anhydrous

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Table 1. NMR Data for Compound CA-14 (1) in CD_3OD at 25 °C

carbon	δ ^1H[a]	δ ^{13}C[b]
1	4.62 (dd, 7.1, 1.4)	38.28
2	2.94 (dd, 15.6, 1.4)	39.26
	3.22 (dd, 15.6, 7.1)	
3		170.02
4a		151.95
5	6.46 (s)	99.19
6		159.39
6a		118.21
7		134.88
8		132.95
9		153.44
10	6.86 (s)	105.09
10a		136.53
10b		108.78
1′		133.66
2′,6′	6.90 (d, 8.5)	129.15
3′,5′	6.67 (d, 8.5)	116.73
4′		157.65
CH_3CO	2.49 (s)	32.69
$COCH_3$		209.85
CH_3Ar	2.72 (s)	20.47

[a] Splitting patterns and J values (Hz) are given in parentheses. [b] Signal assignments were based on ^1H NOE, APT, HETCOR, and COLOC experiments.

Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography (eluent $CHCl_3$:ethyl acetate, 5:0.5) furnished the title compound (**9**) as a pure amorphous solid (140 mg) as determined by TLC analysis (eluent $CHCl_3$:ethyl acetate, 5:1, R_f, 0.53): mp 176−178 °C; IR (nujol) 3360, 1730, 1640, 1600, 1510 cm^{-1}; UV (CH_3-OH) λ_{max} 228 (log ϵ 4.70), 238 (4.71), 306 (3.89), 332 nm (3.64); ^1H NMR (DMSO-d_6) δ 2.91 (brd, J = 15.7 Hz, 1H, H-2a), 3.41 (dd, J = 15.7, 6.8 Hz, 1H, H-2b), 3.70 (s, 3H, OCH_3), 4.94 (brd, J = 6.8 Hz, 1H, H-1), 6.73 (s, 1H, H-5), 6.84 (d, J = 8.6 Hz, 2H, H-3′, H-5′), 7.04 (d, J = 8.6 Hz, 2H, H-2′, H-6′), 7.41 (app t, $\langle J \rangle$ = 7.5 Hz, 1H, H-8), 7.50 (app t, $\langle J \rangle$ = 7.5 Hz, 1H, H-9), 7.76 (d, J = 8.4 Hz, 1H, H-10), 8.18 (d, J = 8.4 Hz, 1H, H-7), 10.63 (s, 1H, 6-OH); relevant NOE associations: from H-1 to H-10 (20.8%), from H-10 to H-1 (15.9%), from H-7 to 6-OH (1.1%), from 6-OH to H-7 (4.6%) and to H-5 (13.1%); ^{13}C NMR (DMSO-d_6) δ: 35.09 (d), 37.63 (t), 54.91 (q), 98.97 (d), 108.63 (s), 114.18 (d), 122.53 (d), 123.04 (d), 123.66 (d), 127.52 (d), 127.73 (d), 131.29 (s), 133.89 (s), 149.49 (s), 154.17 (s), 158.12 (s), 167.41 (s); EI-MS m/z 320 (M^+), 161.

Preparation of the Isomeric Esters 10 and 11. A stirred solution of 4-methoxycinnamic acid (**8**; 2 g, 11.2 mmol), 4-(dimethylamino)pyridine (DMAP; 132 mg, 1.1 mmol), and 1,3-dihydroxynaphthalene (**7**; 2.2 g, 13.9 mmol) in dry CH_2Cl_2 (100 mL) was cooled to 0 °C and treated with 1,3-dicyclohexylcarbodiimide (DCC; 4 g, 19.4 mmol) under N_2. After 1 h, the reaction mixture was allowed to warm to room temperature and was further stirred overnight. The precipitated urea was filtered off, and the filtrate was washed with 1 N HCl (2 × 50 mL) and then with water (2 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. TLC analysis of the residue (eluent, $CHCl_3$: ethyl acetate, 5:1) showed it to contain, besides the diester, two compounds (ratio 2:1) with R_f values of 0.57 and 0.66, respectively. Separation of the mixture by flash chromatography (eluent, $CHCl_3$:ethyl acetate, 10:1) afforded the more polar (780 mg) and the less polar (400 mg) compounds, which were found to be the monoesters **10** and **11**, respectively, on the basis of the following data. For compound **10**: ^1H NMR (DMSO-d_6) δ: 3.84 (s, 3H, OCH_3), 6.88 (d, J = 15.9 Hz, 1H, H-2′), 6.97 (d, J = 2.4 Hz, 1H, H-2), 7.04 (d, J = 8.7 Hz, 2H, H-6′, H-8′), 7.09 (d, J = 2.4 Hz, 1H, H-4), 7.30 (app t, $\langle J \rangle$ = 8.0 Hz, 1H) and 7.45 (app t, $\langle J \rangle$ = 8.0 Hz, 1H) (H-6 and H-7), 7.71 (d, J = 8.4 Hz, 1H) and 7.76 (d, J = 8.2 Hz, 1H) (H-5 and H-8), 7.82 (d, J = 8.7 Hz, 2H, H-5′, H-9′), 7.92 (d, J = 15.9 Hz, 1H, H-3′), 10.49 (s, 1H, 3-OH); relevant NOE associations, from 3-OH to H-2 (11.1%) and H-4 (8.7%); ^{13}C NMR (DMSO-d_6) δ 55.29 (q), 106.86 (d), 111.29 (d), 113.95 (d), 114.40 (d), 120.97 (d), 123.16 (d), 126.20 (d), 126.45 (s), 126.73 (d), 130.54 (d), 134.99 (s), 146.58 (d), 147.26 (s), 154.93 (s), 161.50 (s), 165.11 (s). For compound **11**: ^1H NMR (DMSO-d_6) δ 3.85 (s, 3H, OCH_3), 6.73 (d, J = 1.8 Hz, 1H, H-2), 6.77 (d, J = 16.1 Hz, 1H, H-2′), 7.05 (d, J = 8.7 Hz, 2H, H-6′, H-8′), 7.19 (d, J = 1.8 Hz, 1H, H-4), 7.43−7.56 (m, 2H, H-6, H-7), 7.80 (d, J = 8.7 Hz, 2H, H-5′, H-9′), 7.84 (d, J = 7.6 Hz, 1H, H-5), 7.87 (d, J = 16.1 Hz, 1H, H-3′), 8.15 (d, J = 7.6 Hz, 1H, H-8), 10.49 (s, 1H, 1-OH); relevant NOE associations, from 1-OH to H-8 (3.6%) and H-2 (14.8%) and from H-8 to 1-OH (2.7%); ^{13}C NMR (DMSO-d_6) δ 55.31 (q), 103.75 (d), 109.08 (d), 114.41 (d), 121.99 (d), 122.73 (s), 124.27 (d), 126.47 (s), 126.89 (d), 127.16 (d), 130.45 (d), 134.07 (s), 146.16 (d), 148.59 (s), 154.20 (s), 161.44 (s), 165.19 (s).

Acid-Catalyzed Cyclization of 11. A solution of the monoester **11** (25 mg, 0.078 mmol) and *p*-toluenesulfonic acid (PTSA; 7.5 mg, 0.039 mmol) in 40 mL of toluene was heated at 70 °C for 20 h under N_2. After cooling, the mixture was washed with a saturated $NaHCO_3$ solution (2 × 20 mL) and with water (20 mL), and then dried over anhydrous Na_2SO_4. The residue, obtained on concentration, was chromatographed on silica gel (eluent, $CHCl_3$:ethyl acetate, 5:1) to afford 16 mg (65% yield) of pure compound **9**.

RESULTS AND DISCUSSION

An acetone-chloroform extract of Cape aloe was fractioned by repeated silica gel chromatography followed by DCCC. After a final purification by flash chromatography, a compound, provisionally named CA-14, was obtained as an amorphous powder in 0.05% yield. Its negative-ion FAB MS spectrum displayed a pseudomolecular $[M - H]^-$ anion at m/z 377, and the corresponding molecular formula $C_{22}H_{18}O_6$ was deduced from HR EI-MS data (found 378.1104000, calcd 378.1103386). Three of six oxygen atoms were shown to belong to phenolic hydroxy groups by inspection of the ^1H NMR spectrum recorded in DMSO-d_6 (signals at δ 9.31, 10.08, and 10.39, D_2O exchangeable); in addition, treatment of compound CA-14 with dimethyl sulfate gave a trimethyl ether. The ^{13}C NMR spectrum (Table 1) showed only 20 signals that were found, from an APT experiment, to be due to 2 methyls, 1 methylene, 5 methines, and 12 quaternary carbons. The methine signals at δ 129.15 and 116.73 were significantly more intense than the other methine signals and showed, in the HETCOR spectrum, correlation peaks with the aromatic two-proton doublets at δ 6.90 and 6.67, respectively. This observation clearly indicated the presence of a *para*-disubstituted benzene ring. The ^{13}C NMR spectrum of compound CA-14 also exhibited resonances assignable to a methyl ketone (δ 209.85 and 32.69, the latter signal being correlated with protons at δ 2.49 in the HETCOR spectrum) and to an ester or a lactone group (δ 170.02). The existence of the two carbonyl functions was supported by intense absorption bands at 1667 and 1748 cm^{-1} in the IR spectrum.

The ^1H NMR spectrum of compound CA-14 (Table 1) showed, besides resonances of the *para*-disubstituted benzene ring and of the MeCO group, signals of two aromatic protons (singlets at δ 6.46 and 6.86), of a methyl group (singlet at δ 2.72), and of an ABX system in the aliphatic region due to two nonequivalent geminal protons at δ 2.94 and 3.22 and a benzylic methine proton at δ 4.62. On the basis of these spectroscopic data, together with an electronic absorption spectrum consistent with a polyhydroxylated naphthalene nucleus (Lemli et al., 1981) and biosynthetic considerations concerning the acetate-malonate pathway (O'Hagan, 1991), the structure of 8-acetyl-6,9-dihydroxy-1-(4-hydroxyphenyl)-7-methylbenzo[*f*]chroman-3-one (**1**) could

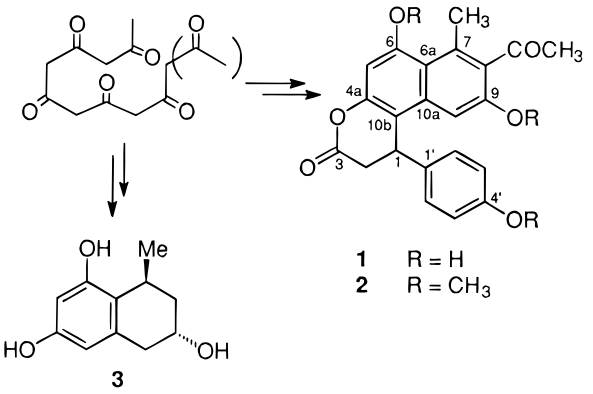


Figure 1. Structure of compound CA-14 (**1**) and presumable biogenesis of its naphthalene moiety.

be assigned to compound CA-14. In particular, irradiation of H-1 resulted in intensity enhancement of the proton signal at δ 6.86, thus indicating the close proximity of the methine proton at C-1 to the naphthalene nucleus. Such a finding ruled out the alternative structure with the dihydropyrone ring fused to the 4a/5 or 5/6 sides of the naphthalene system, and led to the unambigous assignments of H-5 and H-10. The structure **1** was further confirmed by COLOC and NOE experiments, which allowed the relative positions of substituents on the naphthalene nucleus to be definitely established.

It must be pointed out that **1** showed neither a Cotton effect in the CD spectrum nor measurable optical rotation, thus suggesting its occurrence in the drug in racemic form. This was unequivocally proved by achieving resolution of **1** into its enantiomers (1:1 ratio) through reversed-phase HPLC with a chiral (β-cyclodextrin) stationary phase.

The racemic character of **1** strongly supports a nonenzymatic origin of the stereogenic center at C-1. On the other hand, an inspection of its structure (**1**) clearly shows that the carbon skeleton is made up of two biogenetically independent units connected by the C_1-C_{10b} bond [*i.e.*, a polyhydroxylated naphthalene nucleus, from a decarboxylated heptaketide chain (Figure 1) and a phenylpropane residue related to *p*-coumaric acid]. Polyketides as well as *p*-coumaric acid esters are very common among the secondary metabolites occurring in Cape aloe (Speranza et al., 1994). All the considerations just mentioned can be well explained if **1** arises from a thermal acid-catalyzed condensation between a naphthalene metabolite, such as **4,** and *p*-coumaric acid (**5**; Figure 2*a*) or from an equivalent intramolecular reaction of **6** (Figure 2*b*) during processing and/or storage of aloe juice. Really, **4** is unknown, but 5,6,7,8-tetrahydro-8-methyl-1,3,6-naphthalenetriol (**3**; Speranza et al., 1991) and two *O*-glucosylated derivatives of **3** (Speranza et al., 1992) have been isolated from Cape aloe. Two facts that also need to be taken into account are that the fresh aloe juice is acidic in character and its processing to solidification is brought about by prolonged heating (Trease and Evans, 1993).

According to route *a* of Figure 2, the benzochromanone system in **1** should arise from an acid-catalyzed conjugate addition (which, alternatively, can be seen as a β-naphthol alkylation at the α-position) followed by lactonization. Condensations of phenols with cinnamic acids or alkyl cinnamates in acidic media have been reported in many papers. In all cases, very drastic conditions were used; for examples, concentrated sulfuric acid (Liebermann and Hartmann, 1891, 1892), boiling concentrated hydrogen chloride (Simpson and Stephen, 1956), polyphosphoric acid (PPA) at 50−100 °C (Hasebe, 1961a,b, 1962; Chenault and Dupin, 1983; Starkov, 1983; Matsui, 1984; Talapatra et al., 1985, Talapatra et al., 1986), boiling trifluoroacetic acid (Kirtany, 1993), and anhydrous aluminum chloride or zinc chloride (Das Gupta, 1972). A number of different products, besides 2-chromanones, were obtained (*i.e.*, cinnamates, chalcones, flavanones, and indanones) depending on the structures of the reacting molecules and the nature of the catalyst employed. In the naphthalene series, a benzo[*h*]chromanone was prepared by condensation of α-naphthol with methyl cinnamates in the presence of aluminum chloride (Das Gupta and Das, 1973), and the reaction of β-naphthol with methyl cinnamate and zinc chloride (Das Gupta and Das, 1973) or with cinnamic acids in a refluxing mixture of sulfuric acid and acetic acid (Koelsch, 1936; Anjaneyulu et al., 1968) was reported to afford a benzo[*f*]chromanone in moderate yields. 1,3-Dihydroxynaphthalene (**7**) could be regarded as a reliable model molecule for the naphthalene moiety of **1**, so **9** was synthesized in 44% yield by condensation of **7** with *p*-methoxycinnamic acid (**8**) in 1:2 mixture of PPA and toluene at 90 °C (Scheme 1). A large number of byproducts were present in the reaction mixture, but none of them was isolated and characterized. Using the benzo[*f*]chromanone **9** as a reference substance, the condensation just described was tested under milder conditions. However, no reaction was observed in TLC when an equimolecular solution of **7** and **8** (2 mM) in toluene containing *p*-toluenesulfonic acid (1 mM) was kept at 70 °C for 40 h.

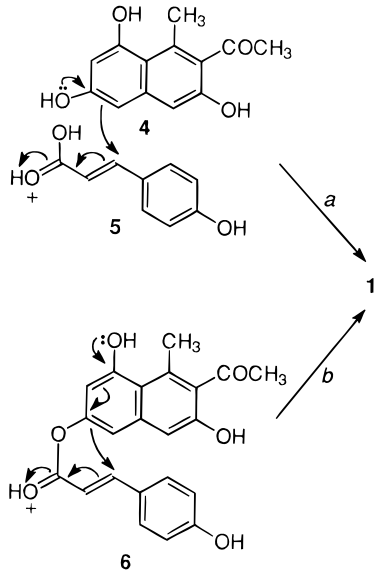
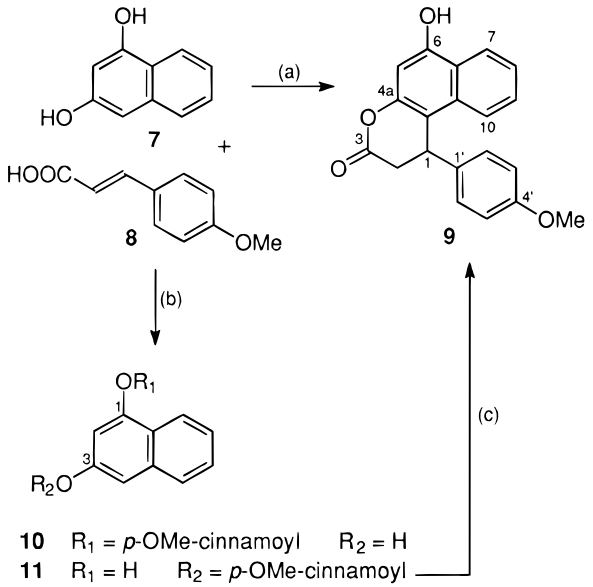


Figure 2. Possible routes to compound CA-14 (**1**).

Considering that a space proximity between the nucleophilic center of the phenol ring and the electrophilic one of the α,β-unsaturated acid could affect the reaction rate, an intramolecular Michael addition (as hypothized in the route *b* of Figure 2) was examined. 1,3-Dihydroxynaphthalene (**7**) was treated with carboxy-activated *p*-methoxycinnamic acid (**8**), and each of the resulting monoesters was isolated by flash chromatography (Scheme 1). The two isomeric *p*-methoxycinnamates were unequivocally distinguished on the basis of the following ^{1}H NOE associations in DMSO-d_6: OH with H-2 and H-8 in **11,** and with H-2 and H-4 in **10**

Scheme 1[a]



[a] Key: (a) PPA, toluene, 90 °C; (b) DCC, DMAP, CH_2Cl_2, r.t.; (c) PTSA, toluene, 70 °C.

(see Materials and Methods). After heating the ester **11** in toluene (2 mM) in the presence of *p*-toluenesulfonic acid (1 mM) at 70 °C for 20 h, the cyclized derivative (**9**) was obtained in 65% yield. The isomer of **9**, resulting from intramolecular attack on C-2 of the naphthalene nucleus, was not found in the reaction mixture.

Entropic assistance and acid catalysis clearly concur to promote the conjugate addition, thus allowing the benzochromanone nucleus to be formed without requiring very strong acid media and high substrate concentrations. In light of these findings, the production of the ester **6** by the plant and its succesive thermal cyclization (Figure 2, route *b*) seem to be the most likely explanation for the occurrence of the racemic **1** in the processed aloe juice.

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