

Schizanthines N, O, and P, Tropane Alkaloids from the Aerial Parts of *Schizanthus tricolor*Munir Humam,[†] Thomas Kehrl,† Damien Jeannerat,[‡] Orlando Muñoz,[§] Kurt Hostettmann,[†] and Philippe Christen*[†]

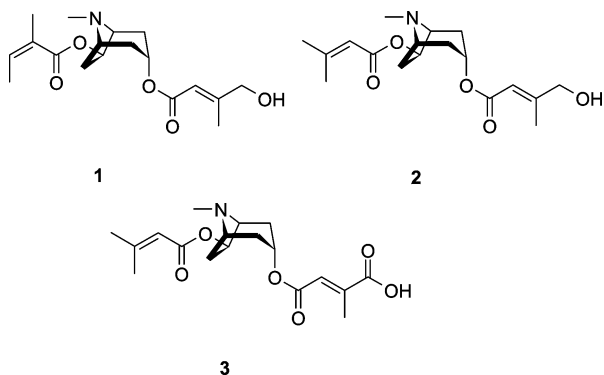
School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland, Department of Organic Chemistry, University of Geneva, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland, and Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile

Received September 8, 2010

Three tropane alkaloids, named schizanthines N, O, and P (**1–3**), have been isolated from the crude alkaloid extract of the endemic Chilean plant *Schizanthus tricolor*. On the basis of extensive NMR studies and MS fragmentation analysis, their structures were determined to be 3 α -(*E*)-4-hydroxyseneciolyloxy-6 β -angeloyloxytropane (**1**), 3 α -(*E*)-4-hydroxyseneciolyloxy-6 β -seneciolyloxytropane (**2**), and 3 α -mesaconyloxy-6 β -seneciolyloxytropane (**3**). Compounds **1** and **2** are the first isomeric alkaloids in the tropane series possessing a hydroxyseneciyl substituent as an esterifying moiety.

Schizanthus tricolor Grau et Gronbach (Solanaceae) is an annual herb that grows up to 60 cm in height and has zygomorphic lilac flowers with yellow trimmed, deep purple centers. It grows in the Valparaíso and Santiago regions in central Chile as well as in the Atacama Desert.¹ The genus *Schizanthus* R. et P. is characterized by the presence of a wide range of tropane alkaloids including derivatives esterified with two series of isomeric C₅ acids, namely, angelic, seneciolic, and tiglic acids, as well as itaconic, mesaconic, and citraconic acids, including dimers and trimers.^{2–6} These esterifications lead to the formation of numerous positional and configurational isomers (Figure 1).

In our continuing studies on Chilean *Schizanthus* species,^{2,7–10} the present investigation describes the isolation and structural determinations of three new tropane alkaloids from a methanolic extract of the aerial parts of *S. tricolor*. Two of them are isomeric compounds having a molecular mass of 337 Da, with seneciyl- and angeloyl-derived substituents. The third is a mesaconyl derivative and has a molecular mass of 351 Da.



Results and Discussion

A preliminary investigation by GC-MS¹⁰ demonstrated the presence of numerous tropane derivatives in the methanolic extract, which was subjected to a series of column chromatographic purification steps on normal- and reverse-phase silica gel to afford two pure isomeric alkaloids: 3 α -(*E*)-4-hydroxyseneciolyloxy-6 β -angeloyloxytropane (**1**) and 3 α -(*E*)-4-hydroxyseneciolyloxy-6 β -seneciolyloxytropane (**2**), as well as 3 α -mesaconyloxy-6 β -seneciolyloxytropane (**3**).

High-resolution electrospray ionization mass spectrometry (HRESIMS) showed pseudomolecular ion peaks at m/z 338.1973 and 338.1971 [M + H]⁺ for **1** and **2**, respectively, indicating a molecular formula of C₁₈H₂₇NO₅ (338.1967 calcd for C₁₈H₂₈NO₅ [M + H]⁺) and two ions at m/z 352.1771 [M + H]⁺ and 350.1593 [M – H][–] for compound **3**, matching the molecular formula C₁₈H₂₅NO₆. Atmospheric pressure-chemical ionization-ion trap-mass spectra (APCI-IT-MS) revealed an ion for **1** and **2** at m/z 256 resulting from a McLafferty rearrangement, confirming the presence of a C₅ acid as a substituent on the tropane skeleton. Peaks at m/z 238, 222, and 122 corresponded to the loss of ester moieties and indicated the presence of two C₅ acids, either angelic, seneciolic, or tiglic acids. The fragmentation of **3** gave an ion at m/z 334 (loss of one molecule of water), indicating the presence of the acidic function. Similarly, peaks at m/z 270, 252, 222, 140, and 122 were generated after the loss of the ester moieties and indicated the presence of two C₅ acids. The gas chromatography-electron impact-mass spectrum (GC-EIMS) of alkaloids **1** and **2** showed a molecular ion peak at m/z 337 and a peak at m/z 122, indicating that the tropane nucleus was disubstituted. Peaks at m/z 320 and 254 resulted from the loss of an OH [M⁺ – OH] and [M⁺ – C₅H₇O] from cleavage of an O–CO bond. The ion at m/z 238 [M⁺ – C₅H₇O₂] revealed loss of a C₅ acid fragment, the presence of which was confirmed by the ion at m/z 222 [M⁺ – C₅H₇O₃], and the loss of two C₅ acid fragments gave the ion at m/z 122 [M⁺ – (C₅H₇O₃) – (C₅H₇O₂)]. Fragmentation patterns were similar for both isomers. The UV spectrum displayed an absorption maximum at 220 nm due to a C₅ α,β -unsaturated acid.

Capillary NMR was used due to the limited amounts of the isolated compounds. The ¹H NMR assignments for **1**, **2**, and **3** were carried out using a combination of 1D and 2D NMR techniques, and the ¹³C chemical shifts originated from the 2D HSQC and HMBC spectra (Table 1). However, the low resolution of the spectra

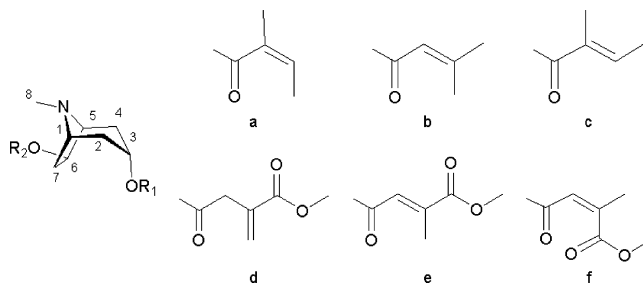


Figure 1. Structures of tropane alkaloids present in the genus *Schizanthus*: (a) angeloyl, (b) seneciyl, (c) tiglyl, (d) methylitaconyl, (e) methylmesaconyl, and (f) methylcitraconyl moieties (R₁/R₂).

* To whom correspondence should be addressed. Tel: +41 22 379 65 61. Fax: +41 22 379 33 99. E-mail: philippe.christen@unige.ch.

[†] School of Pharmaceutical Sciences, University of Geneva, University of Lausanne.

[‡] Department of Organic Chemistry, University of Geneva.

[§] Departamento de Química, University of Chile.

Table 1. NMR Spectroscopic Data (500 MHz, CD₃OD, δ in ppm) for Compounds **1–3** Obtained Using Capillary NMR

position	1		2		3	
	δ_C^a	δ_H	δ_C^a	δ_H	δ_C^a	δ_H
1	61.4 CH	3.76 s	61.9	3.92 s	60.0 ^c	4.02 s
2	33.7 CH _{endo} CH _{exo}	2.34 s 1.94 s	33.4	2.39 br s 2.02 s	2.43 br s	2.29–2.31 br s
3	64.3 CH	5.08, s	63.8	5.10 s	62.5 ^a	5.14 s
4	32.3 CH _{endo} CH _{exo}	2.38 br s 2.14 s	31.9	2.43 br s 2.22 s	2.39–2.43 br s	2.14 s
5	66.9 CH	3.63 s	67.4	3.79 s	66.0 ^c	3.90 s
6	76.5 CH	5.64 s	74.8	5.62 s	78.0 ^a	5.64 s
7	34.2 CH _{endo} CH _{exo}	2.83 br s 2.38 br s	34.3	2.88 s 2.36 br s	2.95 s	2.41–2.43 br s
8	39.0 CH ₃ N	2.77 s	38.5	2.88 s	38.5 ^a	2.95 s
9	165.5 ^b qC		165.5 ^b			
10	112.4 CH	6.05 s	112.3	6.05 s	119.5 ^c	6.55 s
11	160.5 ^c qC		160.7 ^c		154.0 ^c	
12	65.9 CH ₂ OH	4.10 s 3.33 s	65.8	4.11 s 3.36 s	174.0 ^c	
13	14.6 CH ₃	2.11 s	14.7	2.11 s	14.6 ^a	2.31 s
9'	167.4 ^c qC		166.3 ^b		178.5 ^c	
10'	127.3 ^c qC/CH		114.8	5.74 s	115.5 ^c	5.75 s
11'	139.0 CH/qC	6.19 s	159.3 ^c		157.0 ^{a,c}	
12'	19.4 CH ₃	1.91 s	19.3	2.19 s	19.0 ^c	2.19 s
13'	26.1 CH ₃	2.01 s	26.3	1.95 s	26.2 ^c	1.95 s

^a Based on HSQC. ^b Based on standard ¹³C NMR spectra measured in CDCl₃ for the isomer mixture (isomer subfraction). ^c Based on HMBC.

recorded from the microcoil probe precluded determination of the coupling constants. Thus, a 5 mm quadruple nuclei probe (QNP) was used as well to record NMR spectra of the isomer mixture (**1** and **2**) to obtain structurally important information (¹³C, ¹H–¹H coupling constants and weak HMBC signals).

Thus, the nature of the α,β -unsaturated ester side chains of **1**, **2**, and **3** was ascertained unambiguously. The ¹H NMR spectrum of compound **1** showed three methyl singlets [δ_H 1.91 (H₃-12'), 2.01 (H₃-13'), and 2.11 (H₃-13)] and a methylene group at δ 4.10 (H₂-12) characteristic of a CH₂OH moiety with the OH proton resonating as a singlet at δ 3.33. Two methines showed resonances at δ 6.05 (H-10) and 6.19 (H-11'). The chemical shifts characteristic of sp² carbons of α,β -unsaturated esters allowed us to assign the carbons 9 (165.5), 9' (167.4) to carbonyls, 10 (112.4), 10' (127.3) to α and 11 (160.5), 11' (139.0) to β positions. The quaternary carbons 10' and 11 led to the conclusion that the side chains were angelico and hydroxysenecioic esters, respectively. The position of the OH group in the hydroxysenecioic ester moiety was determined by comparing the observed NMR chemical shifts with those found in the literature^{11,12} and were located (*E*)-4 with respect to the carbonyl. A *Z* configuration is very unlikely because this side chain would be expected to fragment to the lactone through intramolecular nucleophilic displacement. This is the first time that a hydroxysenecioyl moiety has been encountered in tropane alkaloids of *Schizanthus* species. The core of compound **1** had a tropane skeleton. Two methine and one methyl group linked to the nitrogen atom were observed at δ_H 3.76 (H-1), 3.63 (H-5), 2.77 (H₃C-N), δ_C 61.4 (C-1), and 66.9 (C-5). The ¹³C chemical shift of the H₃C-N (39.0) indicated that the methyl is in the equatorial position.¹³ The three methylene groups observed at δ_H 2.34, 1.94 (H_{endo}, H_{exo}-2), 2.38, 2.14 (H_{endo}, H_{exo}-4), and 2.83, 2.38 (H_{endo}, H_{exo}-7), as well as the two deshielded methine groups located at δ_H 5.08 (H β -3) and 5.64 (H_{endo}-6), δ_C 64.3 (C-3) and 76.5 (C-6), indicated a 3,6-disubstituted tropane nucleus. The configuration of the tropane moiety (*3R,6R* or *3S,6S*) was determined by circular dichroism (CD) spectroscopy.¹⁴ The orientation of substituents relative to the tropane skeleton was deduced from the signal multiplicity and coupling constants of the proton spectrum. The triplet of H-3 (*J* = 4.9 Hz) indicated α -orientation of the substituent at C-3.^{15,16} Orientation of the substituent at C-6 was established by analysis of the coupling constants of the H_{endo}-7, H_{exo}-7, and H-5 protons. The H-6 proton

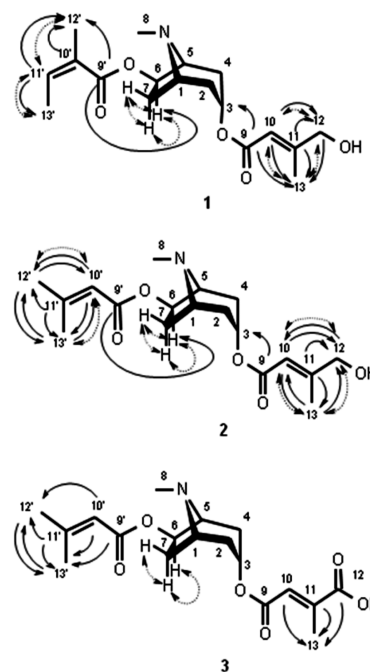
Table 2. COSY and HMBC Data of Compounds **1–3** Obtained Using Capillary NMR

position	¹ H–		¹ H–		¹ H–	
	¹ H COSY	HMBC	¹ H COSY	HMBC	¹ H COSY	HMBC
1	2 _{exo} , 7 _{endo}	CH ₃ -N	2 _{exo} , 7 _{endo}	CH ₃ -N		
2 _{endo}	1, 2 _{exo} , 3		1, 2 _{exo} , 3		2 _{exo}	
2 _{exo}	2 _{endo}		2 _{endo}		2 _{endo}	
3	2 _{endo} , 4 _{endo}		2 _{endo} , 4 _{endo}			
4 _{endo}	3, 4 _{exo} , 5		3, 4 _{exo} , 5		4 _{exo}	
4 _{exo}	4 _{endo} , 5		4 _{endo} , 5		4 _{endo}	
5	4 _{endo} , 4 _{exo}	CH ₃ -N	4 _{endo} , 4 _{exo}	CH ₃ -N		CH ₃ -N
6	7 _{endo} , 7 _{exo}		7 _{endo} , 7 _{exo}		7 _{endo}	
7 _{endo}	6, 7 _{exo}		6, 7 _{exo}		6, 7 _{exo}	
7 _{exo}	6, 7 _{endo}		6, 7 _{endo}		7 _{endo}	
10	12, 13	12, 13	12, 13	12, 13		13
11		12, 13		12, 13		13
12	10	10, 13	10			13
13	10		10			
9'			12'			13'
10'	12', 13'	12', 13'		12'		12', 13'
11'		12', 13'	12', 13'	12', 13'		12', 13'
12'	10'	10', 13'	11'	13'		
13'	10'		11'			12'

showed two couplings (7.68, 3.02 Hz) with both H-7 and no coupling with the vicinal H-5. This observation implied β orientation (*exo*) of the substituent.^{17–19}

Unambiguous assignments of the side-chain positions were obtained from the HMBC spectrum of the sample containing the mixture of isomers analyzed using a 5 mm QNP probe. The long-range ¹H–¹³C correlations of H-3 with the carbonyl of hydroxysenecioic acid and of H-6 with the carbonyl of angelico acid led to the conclusion that **1** was 3 α -(*E*)-4-hydroxysenecioyloxy-6 β -angeloyloxytropane. The correlations observed in the 2D COSY and HMBC spectra are shown in Table 2 and Figure 2.

The NMR spectra of **2** were very similar to those of **1**. They differed only in a methyl position of the C-6 substituent. The HSQC spectrum of **2** showed that the chemical shift of C-10' at δ 114.8 corresponded to a methine α to the carbonyl, whereas the methine was β in **1**. Hence, the structure of **2** was elucidated as 3 α -(*E*)-4-hydroxysenecioyloxy-6 β -senecioyloxytropane. The NMR spectra

**Figure 2.** Selected ¹H–¹H COSY (dashed arrows) and ¹H–¹³C HMBC (full arrows) correlations observed for compounds **1**, **2**, and **3**.

of **3** were very similar to those of **2** except that the chemical shift of C-12 resonated at δ 174.0, which is typical of an α,β -unsaturated carboxylic acid. The chemical shifts of C-11 and C-12 corresponded to what was expected when replacing a CH₂OH function with a COOH group. Thus, the structure of **3** was elucidated as 3 α -mesaconyloxy-6 β -seneciolyloxytropone (Table 1). We suggest that these three tropane alkaloids be named schizanthine N (**1**), schizanthine O (**2**), and schizanthine P (**3**).

Schizanthines N, O, and P have not been previously described in the literature. The observation of new hydroxyseneciolyloxy tropane derivatives illustrates the variety of tropane alkaloids found in the *Schizanthus* genus.

The genus *Schizanthus* is characterized by the presence of 3,6-dihydroxytropone derivatives esterified with mono- (angelic, seneciolic, tiglic) and dicarboxylic (itaconic, mesaconic, citraconic) C₅ acids leading to numerous positional isomers.² Dimers and one trimer have also been identified previously.³ In this study, it is noteworthy that in two of the alkaloids (**1**, **2**) incorporation of the biogenetically (*E*)-4-hydroxyseneciolyloxy esterifying moiety at the 3-position is reported for the first time. Other esterifying variants incorporating this acid might be expected to be found in the future in this genus.

To date, no study has been published regarding the biosynthesis of these alkaloids nor why these compounds exist in this particular genus. If this is due to nonspecific esterase reactions as suggested for *Datura*,²⁰ it remains to be proved.

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a Perkin-Elmer 241 MC polarimeter (MeOH, *c* in g/100 mL). UV spectra were recorded on a Perkin-Elmer Lambda-20 UV-vis spectrophotometer (Wellesley, MA) in MeOH. CD spectra (0.1 mM in MeOH) were measured on a JASCO J-715 spectrometer (Easton, MD). Capillary NMR spectra were recorded on a Varian Unity Inova 500 MHz spectrometer (Palo Alto, CA) with a CapNMR probe from Protasis/MRM (Savoy, IL) by direct injection of 7 μ L samples in CD₃OD. The assignment of protons was determined using ¹H and COSY spectra, while ¹³C data came from HSQC and HMBC experiments. The ¹H spectrum used for the measurements of the coupling constants and the HMBC spectrum used for the determination of substituent position were recorded in CDCl₃ on a Bruker-DRX 500 MHz ¹H Larmor frequency (Dübendorf, Switzerland) using a 5 mm QNP direct detection probe. Chemical shifts (δ) are in ppm relative to SiMe₄ as internal standard, and coupling constants (*J*) are in Hz. GC-MS analyses were carried out using a Hewlett-Packard chromatograph 5890 series II coupled to a HP 5972 mass-selective detector (Agilent Technologies, Palo Alto, CA). The MS transfer line was set at 280 °C. The MS detector was used in the electron impact ionization (EI mode at 70 eV). Mass spectra were recorded in the range 30–600 Da at 1.3 scan/s. The capillary column (HP5-MS, 30 m \times 0.25 mm i.d., 0.25 μ m film thickness) was used with He as carrier gas under the following conditions: an initial oven temperature of 70 °C was maintained for 1 min, then linearly increased at 5 °C/min to 285 °C, and held at this temperature for 15 min. A sample volume of 1 μ L was injected in the splitless mode into a laminar liner at 250 °C using a fast HP 6890 series autosampler. Retention indices were determined in the split mode (15:1) and calculated using a linear gradient temperature from 70 to 285 at 5 °C/min and held at this temperature for 15 min. LC-UV-APCI-MS analysis was performed on an Agilent 1100 series liquid chromatograph system fitted with a Zorbax Extend C-18 column (150 \times 4.6, 3.5 μ m, Agilent) and with a photodiode array detector connected to a Finnigan MAT LCQ ion trap mass spectrometer (San Jose, CA) equipped with a single quadrupole ion trap mass analyzer. The APCI parameters were as follows: capillary temperature 150 °C, capillary voltage 10 V, vaporizer temperature 450 °C, positive detection mode, sheath gas N₂, sheath gas flow rate 80 psi, discharge current 5 μ A, mass detection (150–900 Da). High-resolution electrospray ionization mass spectra (HRESIMS) were obtained on a UPLC/MS Waters Acquity 2996 system coupled with a LCT Premier Waters Micromass time-of-flight (TOF) mass spectrometer (Milford, MA) by direct injection (5 ng/mL; water +0.1% formic acid in acetonitrile). TLC was performed on Merck precoated silica gel 60 F₂₅₄ plates, and spots were

visualized under UV light and by spraying with Dragendorff's reagent. Low-pressure liquid chromatography was carried out using an Ismatec pump (Glattbrugg, Switzerland) with Lobar LiChroprep Si 60 (440 \times 37 mm, Merck) and Lobar LiChroprep RP-18 (310 \times 25 mm, Merck) columns. Compounds were monitored with a Knauer variable-wavelength monitor and a LKB Bromma 2210 recorder. Semipreparative HPLC was performed first on a Varian 9012 solvent delivery system equipped with a Varian 230 ProStar UV-vis detector with a Symmetry Prep C-18 column (150 \times 19 mm, 7 μ m, Waters), then with a Shimadzu LC-8 pump equipped with a Knauer UV detector with a NovaPak C-18 repacked radial-compression column (150 \times 8 mm, 7 μ m; Waters). The detection was performed at 220 nm.

Plant Material. The aerial parts of *S. tricolor* were collected in December 2003 on the Cachagua Beach, Quinta Region (Valparaíso, Chile), and identification was confirmed by Prof. Fernanda Pérez (Departamento de Botánica, Universidad de Chile, Santiago). A voucher specimen has been deposited at the Facultad de Ciencias Químicas (no. 2000-3).

Extraction and Isolation. The plant material (1.3 kg) was extracted successively with hexane (3 \times 2.5 L) and MeOH (3 \times 2.2 L) at room temperature as already described.² After filtration, the MeOH solution was evaporated to dryness. The residue (161.2 g, 12.4%) was suspended in 0.1 M HCl (0.8 L), filtered, and extracted with Et₂O (3 \times 1.2 L). The aqueous solution was basified with 4% NH₄OH (1.5 L) to pH 12 and then extracted with CH₂Cl₂ (3 \times 0.6 L). The CH₂Cl₂ extract was dried with anhydrous Na₂SO₄, filtered, and evaporated, yielding 3.7 g (0.28%) of a gummy alkaline residue. A portion of this residue (2.5 g) was first fractionated by low-pressure chromatography on Lobar silica gel eluted with EtOAc–MeOH–3% NH₄OH (20:2:1). Thirteen fractions (A–M) were obtained following GC-MS and LC-MS analyses. Fractions E and F were combined (270 mg) and further separated on a Lobar RP-18 column using a solvent gradient of alkaline H₂O–MeOH (10 to 100%) (pH 8), which gave 22 fractions (1–22). According to mass spectrometry monitoring, fraction 2 was subjected to semipreparative column chromatography on a Symmetry Prep C-18 column using acidic 50% MeOH (pH 3) to give a mixture of **1** and **2** (13 mg). Fraction 3 gave compound **3** (200 μ g) under the same conditions. The isolation of isomers **1** and **2** was performed on a radial compression analytical NovaPak C-18 column using isocratic acidic 16% MeOH (pH 3) to yield **1** (550 μ g) and **2** (700 μ g).

3 α -(*E*)-4-Hydroxyseneciolyloxy-6 β -angeloyloxytropone (1**):** colorless oil; [α]_D²⁵ –6.25 (MeOH, *c* 0.04); UV (MeOH) λ_{\max} (log ϵ) 220 nm (2.6); ¹H NMR and ¹³C NMR, see Table 1; RI_{PT} = 2492.4; EIMS *m/z* (rel int) 337 [M]⁺ (1), 320 (1), 238 (3), 222 (5), 138 (12), 122 (28), 96 (15), 95 (76), 94 (100), 83 (14), 82 (13); CIMS *m/z* 256 (62), 238 (14), 222 (91), 140 (48), 122 (100); HREIMS *m/z* 338.1973 (C₁₈H₂₈NO₅ [M + H]⁺, requires 338.1967).

3 α -(*E*)-4-Hydroxyseneciolyloxy-6 β -seneciolyloxytropone (2**):** colorless oil; [α]_D²⁵ –8.0 (MeOH, *c* 0.05); UV (MeOH) λ_{\max} (log ϵ) 220 nm (2.6); ¹H and ¹³C NMR, see Table 1; RI_{PT} = 2548.6; EIMS *m/z* 337 [M]⁺ (1), 320 (1), 238 (2), 222 (4), 138 (12), 122 (25), 96 (15), 95 (80), 94 (100), 83 (24), 82 (10); CIMS *m/z* 256 (62), 238 (14), 222 (91), 140 (48), 122 (100); HREIMS *m/z* 338.1971 (C₁₈H₂₈NO₅ [M + H]⁺, requires 338.1967).

3 α -Mesaonyloxy-6 β -seneciolyloxytropone (3**):** colorless oil; [α]_D²⁵ –3.75 (MeOH, *c* 0.02); UV (MeOH) λ_{\max} (log ϵ) 220 (2.6); ¹H and ¹³C NMR, see Table 1; CIMS *m/z* 334 (5), 270 (100), 252 (52), 222 (35), 140 (22), 122 (83); HREIMS *m/z* 352.1771 (C₁₈H₂₆NO₆ [M + H]⁺ requires 352.1760), *m/z* 350.1593 (C₁₈H₂₄NO₆ [M – H][–] requires 350.1604).

Acknowledgment. We thank Dr. K. Ndjoko for experimental capillary NMR spectra measurement, Mr. A. Pinto for the technical assistance in measuring standard NMR spectra, and Dr. T. A. Bartholomeusz for critical reading of the manuscript.

Supporting Information Available: APCI-IT-MS fragmentation pathways as well as ¹H NMR, COSY, HMBC, and HSQC of compounds **1–3**. This information is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- Perez, F. Evolución de la integración floral en el género *Schizanthus* (Solanaceae) en asociación a los sistemas de polinización. Ph.D. Thesis, Universidad de Chile, Santiago, 2004; p 10.

- (2) Cretton, S.; Glauser, G.; Humam, M.; Jeannerat, D.; Munoz, O.; Maes, L.; Christen, P.; Hostettmann, K. *J. Nat. Prod.* **2010**, *73*, 844–847.
- (3) Griffin, W. J.; Lin, G. D. *Phytochemistry* **2000**, *53*, 623–637.
- (4) Lounasmaa, M.; Tamminen, T. In *The Tropane Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 44, Chapter 1, pp1–114.
- (5) Munoz, O.; Schneider, C.; Breitmaier, E. *Liebigs Ann. Chem.* **1994**, 521–522.
- (6) Pena, R. C.; Munoz, O. *Biochem. Syst. Ecol.* **2002**, *30*, 45–53.
- (7) Bieri, S.; Munoz, O.; Veuthey, J.-L.; Christen, P. *J. Sep. Sci.* **2006**, *29*, 96–102.
- (8) Bieri, S.; Varesio, E.; Munoz, O.; Veuthey, J.-L.; Christen, P. *J. Pharm. Biomed. Anal.* **2006**, *40*, 545–551.
- (9) Bieri, S.; Varesio, E.; Veuthey, J.-L.; Munoz, O.; Tseng, L.-H.; Braumann, U.; Spraul, M.; Christen, P. *Phytochem. Anal.* **2006**, *17*, 78–86.
- (10) Humam, M.; Munoz, O.; Christen, P.; Hostettmann, K. *Nat. Prod. Commun.* **2007**, *2*, 743–747.
- (11) Bourguignon, J.-J.; Schoenfelder, A.; Schmitt, M.; Wermuth, C.-G.; Hechler, V.; Charlier, B.; Maitre, M. *J. Med. Chem.* **1988**, *31*, 893–897.
- (12) Khan, A. T.; Blessing, B.; Schmidt, R. R. *Synthesis* **1994**, 255–257.
- (13) Yagudaev, M. R.; Aripova, S. F. *Chem. Nat. Compd.* **1986**, *22*, 74–78.
- (14) Humam, M.; Christen, P.; Munoz, O.; Hostettmann, K.; Jeannerat, D. *Chirality* **2008**, *20*, 20–25.
- (15) Agar, J. T. H.; Evans, W. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1550–1553.
- (16) El-Iman, Y. M. S.; Evans, W. C.; Grout, R. J.; Ramsey, K. P. A. *Phytochemistry* **1987**, *26*, 2386–2389.
- (17) Al-Said, M. S.; Evans, W. C.; Grout, R. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 957–959.
- (18) Al-Said, M. S.; Evans, W. C.; Grout, R. J. *Phytochemistry* **1989**, *28*, 671–673.
- (19) Bringmann, G.; Günther, C.; Mühlbacher, J.; Lalith, M. D.; Gunathilake, P.; Wickramasinghe, A. *Phytochemistry* **2000**, *53*, 409–416.
- (20) Robins, R. J.; Bachmann, P.; Robinson, T.; Rhodes, M. J. C.; Yamada, Y. *FEBS Lett.* **1991**, *292*, 293–297.

NP1005423