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Synthesis and chemical shifts of five new rotenoids.

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Abstract
Five new rotenoids are prepared using the synthetic approach developed by Pastine and Sames with some modifications. The ^{1}H and ^{13}C NMR resonances were assigned completely with certainty using a concerted application of one- and two-dimensional experiments (DEPT; gs-COSY, gs-HMQC and gs-HMBC).
Keywords: ^{1}H NMR; ^{13}C NMR; COSY; DEPT; HMQC, HMBC; Rotenoids.

1. Introduction

Rotenoids are rotenone derivative compounds (Laforge & Haller, 1932;Crombie, 1963). Many natural rotenoids are extracted from the tropical plants of the *Fabacae* family like *Derris elliptica* (Ahmad-Junan et *al*, 1992), *Derris trifoliate* (Ito et *al*, 2004), *Indigofera tinctoria* (Kamal et *al*, 1993)…etc.

Rotenoids have been extensively studied since many decades for their pharmacological properties: insecticide (Burgos & Redfearn, 1965), antifeedant (Nawrot et *al*, 1989), antiviral (Takatsuki et *al*, 1969) or anticancer (Undeani et *al*, 1997).

Many synthetic routes leading to rotenoids are described in the literature (Ahmad-Junan et *al*, 1992; Amos & Whiting, 1987). This paper reports firstly synthesis given best yields and based on two key cyclisations (Pastine & Sames, 2003) and, secondly, the NMR chemical shifts (^{1}H and ^{13}C) obtained from one- and gradient-selected two-dimensional NMR techniques for five rotenoids (Figure 1).

2. Results and discussion

2.1 Synthesis

The synthesis of rotenoids **6a-e** (Table 1 for the nature of substituents) started with the preparation of the two propargylic ethers **1** needed for the synthesis of the compounds **2a-e** (Figure 2). Treatment of

compounds **1** with *n*-BuLi in anhydrous THF, followed by reaction with conveniently substituted aldehydes, gave the expected acetylenic alcools **2a-e** with a very good yield (92-95%).

The oxidation of compounds **2a-e** into the acetylenic ketone **3a-e** according to the experimental procedure proposed by Pastine and Sames [12] was not very efficient. Indeed, when MnO_2 is used as oxidative agent, the reaction failed or a very low yield was observed. The ketone **3a-e** were obtained with a moderate yield (50-66%) using CrO_3 with a catalytic amount of H_2SO_4 in dry DMF at 20°C (Snatzke, 1961).

The platinum-catalysed 6-endo hydroarylation of the products **3a-e** was realized using $PtCl_4$ as catalyst (5 mol%) in anhydrous toluene and gave the compounds **4a-e** with 35 to 56% yield. In this reaction, when $PtCl_2$ is used instead of $PtCl_4$, a lower yield is observed (28-35%).

Compounds **4a-e** were converted to the ketones **5a-e** in variable yields by demethylation with boron trichloride in anhydrous CH_2Cl_2 at -78°C. This reaction is not very efficient for the compounds including a second methoxy group (**5a** and **5b**). For the compounds **5c**, **5d** and **5e** a good yield is observed (78-83%).

Finally, rotenoids **6a-e** were obtained with a good yield (66-80%) via a cyclisation reaction realised through an oxo-Michael addition in mild basic conditions.

2.2 NMR assignments

The ^{13}C and ^{1}H chemical shifts for compounds **6a-e** are presented in Tables 2 and 3 respectively, and selected proton-proton coupling constants in Table 4.

The ^{1}H and ^{13}C chemical shifts of these compounds were determined in a straightforward manner using chemical shift considerations and concerted application of DEPT-135, COSY, HMQC and HMBC experiments.

The total assignments for all compounds have been realized. However, for the compound **6b**, the distinction between H-7 and H-9 has not been possible. The chemical shift of H-4 is deshielded when C-2/C-3 annelation is introduced. For the compound **6c**, H-17 is strongly deshielded in comparison to the compounds **6d** and **6e**.

The C-7 was assigned with the DEPT-135 sequence. As expected it can be seen that the presence of a methoxy group in the 3-position leads to the deshielding of C-1 (**6a** and **6b** compared to **6c**, **6d** and **6e**). The chemical shift of C-11 is dependant of the type of substitution and is strongly shielded when a C-12/C-13 annelation is introduced.

3. Experimental section

3.1 General

Tetrahydrofuran and diethyl ether were distilled under argon over sodium in the presence of benzophenone. Hexane was distilled over sodium. Dichloromethane was distilled in the presence of di-Phosphorous pentoxide (P_2O_5). Products were purified by chromatography on silica gel using hexane and ether as eluent. All new compounds gave satisfactory elemental analysis (C, H, O).

The reactions were monitored by thin-layer chromatography on aluminium plates precoated with Merck silica gel 60 F254 (0.25 mm). Column chromatography (CC) was performed on silica gel 60 (230 - 400 mesh). The new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy and gas chromatography (GC). Mass spectrometer coupling with GC were made with a HP 5973 apparatus with HP-5 5% Phenylmethylsiloxan column using helium as a vector gas. Elemental analysis were made by "Spectropole" (Aix-Marseille III University-France). Melting points (Mp in °C) were measured with Electrothermal IA 9100.

3.2 NMR spectra

Experiments were performed in 5 mm tubes on a Bruker AC-250 spectrometer (^{1}H: 250 MHz; ^{13}C: 63 MHz) in $CDCl_3$ and acetone-D6 solutions (concentration was 10 mg.mL^{-1}) at 300 K and tetramethylsilane (TMS) was used as an internal standard. Proton coupling constant were extracted from the resolution-enhanced ^{1}H spectrum using Gaussian multiplication technique Ferrige & Lindon, 1978). Resonance multiplicities for ^{13}C were established via the acquisition of DEPT spectra (Doddrell et *al*, 1982). For the DEPT sequence, the width of a ^{13}C 90°C pulse was 7µs, that of a ^{1}H 90°C pulse was 7µs and the $(2J)^{-1}$delay was set at 3.4 ms. For two-dimensional experiments an inverse probehead incorporating a shielded Z-gradient was used. The gradients were amplified by a Bruker BSMS GAB gradient amplifier BD.

gs-COSY spectra were obtained using a pulse sequence (cosy11gs in the operating Bruker software) which includes a 1:1 gradient combination (Hurd, 1990). The spectral widths were 10 ppm and the spectra were collected as 2K × 256 blocks of data. Zero filling was applied in F_1 in order to have a symmetrical matrix of 512 × 512 real data points, which was processed in each by unshifted sinusoidal windows.

The gs-HMQC spectra (inv4gs in the Bruker software) resulted from a 1024 × 1024 data matrix size with 16-32 scans per t_1 depending on the sample concentration, an inter-pulse delay of 3.2 ms and a 5:3:4 gradient combination (Hurd & John, 1991). gs-HMBC spectra were acquiered using a pulse sequence optimized on ^{2}J or ^{3}J couplings

(inter-pulse delay for the evolution of long range couplings: 65 ms) and the same gradient ratio as described above for HMQC experiments (Wilker et *al*, 1993).

3.3 Experimental protocols

When not described, the experimental procedures for the synthesis of different intermediates are those described by Pastine and Sames (Pastine & Sames, 2003).

Ketones **3a-e**

CrO_3 (5.04 mmol, 0.48 g) was slowly added to a solution of acetylenic alcohol (2.52 mmol) in 15 mL of dry DMF. Then 5 drops of concentrated H_2SO_4 was added to the mixture. After stirring at room temperature for 40 min., water (20 mL) and Et_2O (30 mL) was added and the aqueous phase was extracted with Et_2O. The combined organic layers was washed with satured solution of NaCl, dried ($MgSO_4$) and concentrated under reduce pressure. The residue was purified by CC (85% n-hexane and 15% Et_2O).

Demethylated ketones **5a-e**

A 1M solution of BCl_3 (1.2 mmol) was slowly added, under argon at -78°C, to a solution of compounds **4a-e** (1.01 mmol) in 25 mL of dry CH_2Cl_2. After stirring for 1h, the mixture was quenched with satured solution of NH_4Cl (15 mL), extracted with AcOEt and the combined organic layers dried ($MgSO_4$) and concentrated under reduce pressure. The residue was purified by CC (90% *n*-hexane and 10% Et_2O).

Rotenoids **6a-e**

A solution of demethylated ketones **5a-e** (0.3 mmol) in 10 mL of ethanol was satured with potassium acetate. The mixture was heated under reflux for 1h. After cooling at room temperature AcOEt (20 mL) and H_2O (10 mL) was added. The aqueous layer was extracted with AcOEt and the combined organic layers washed with satured solution of NaCl, dried ($MgSO_4$) and concentrated under reduce pressure. The residue was purified by CC (*n*-hexan/Et_2O using different percentage).

Rotenoid **6a**:
Yellow oil. Yield 66%. Elemental analysis (%): Calculated (C: 72.33, H: 5.00, O: 22.67) ; Found (C: 72.36, H: 4.98, O: 22.66).
Rotenoid **6b**:
Yellow solid. Mp 179.2. Yield 80%. Elemental analysis (%): Calculated (C: 75.89, H: 4.85, O: 19.26); Found (C: 75.91, H: 4.82, O: 19.27).
Rotenoid **6c**:
White solid. Mp 155.7. Yield 76%. Elemental analysis (%): Calculated (C: 81.80, H: 4.58, O: 13.62) ; Found (C: 81.77, H: 4.63, O: 13.6).
Rotenoid **6d**:
White solid. Mp 209.3. Yield 68%. Elemental analysis (%): Calculated (C: 79.46, H: 4.67, O: 15.88); Found (C: 79.43, H: 4.68, O: 15.89).
Rotenoid **6e**:
Grey solid. Mp 238.4. Yield 71%. Elemental analysis (%): Calculated (C: 63.01, H: 3.44, O: 12.59, Br: 20.96); Found (C: 62.98, H: 3.47, O: 12.64).

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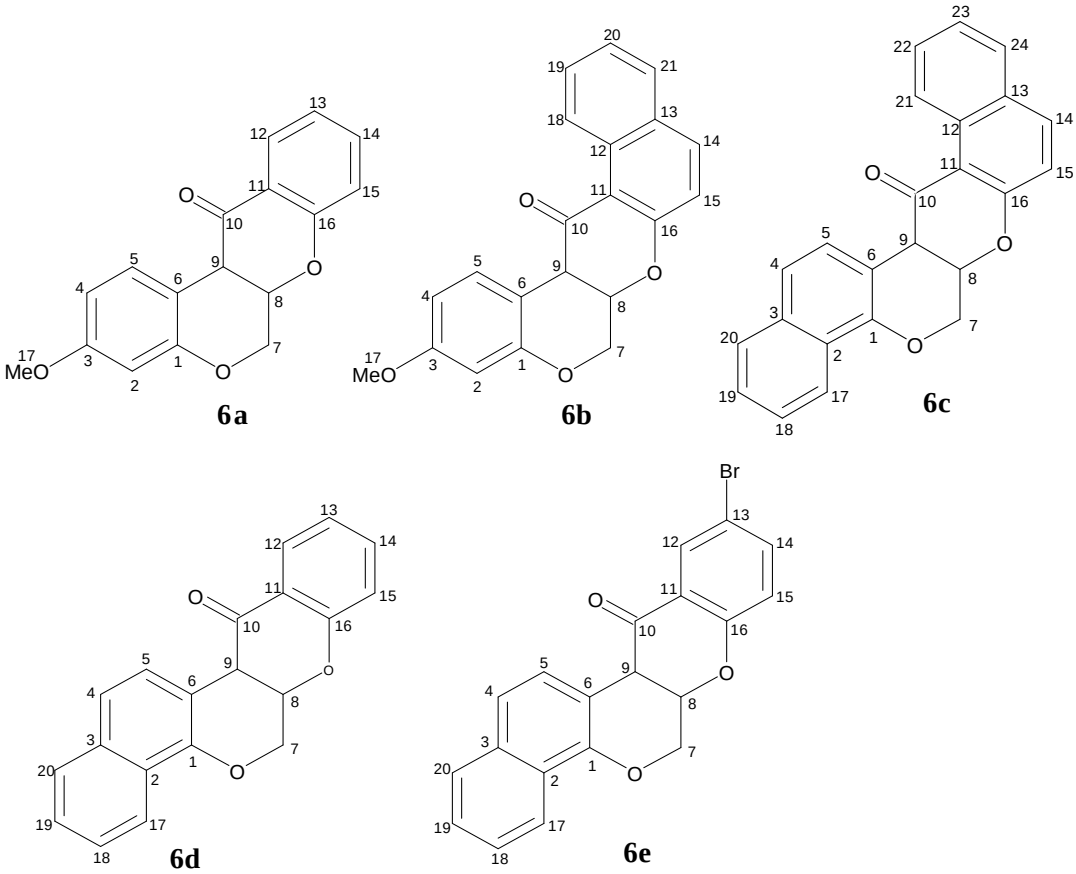

Figure 1. Structure of rotenoids **6a-e** (numbers of atoms were assigned to facilitate comparison of the chemical shifts).

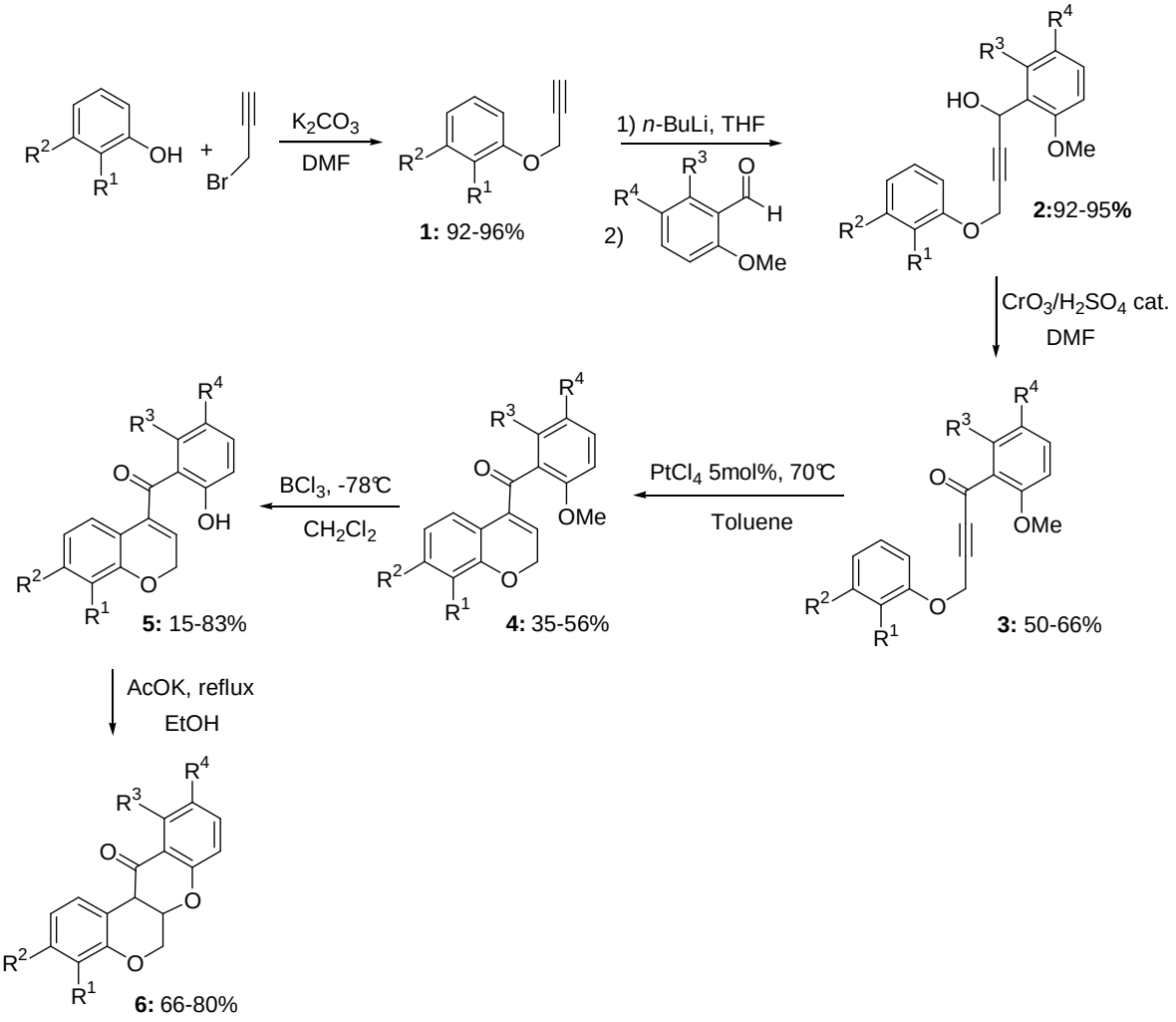

Figure 2. Synthetic pathway to the substituted rotenoids.

Table 1. Nature of substituents for the compounds **a** to **e** .

Compounds	R^1	R^2	R^3	R^4
a	H	OMe	H	H
b	H	OMe		
c				
d			H	H
e			H	Br

Table 2. ^{13}C NMR chemical shifts of rotenoids **6a-e**[i]

Atom	**6a**[ii]	**6b**[ii]	**6c**[ii]	**6d**[iii]	**6e**[ii]	Atom	**6a**[ii]	**6b**[ii]	**6c**[ii]	**6d**[iii]	**6e**[ii]
C-1	160.3	158.8	154.8	151.3	147.4	C-13	117.9	129.9	130.5	122.3	112.8
C-2	102.0	103.1	124.4	126.7	124.1	C-14	136.4	136.7	134.2	136.7	137.6
C-3	160.5	160.2	136.9	135.9	132.3	C-15	118.9	129.2	117.5	115.1	118.4
C-4	105.8	105.3	127.2	120.6	119.4	C-16	154.3	153.7	161.7	160.6	157.8
C-5	127.6	118.2	120.8	118.1	118.6	C-17	52.1	55.7	126.4	126.7	120.2
C-6	108.2	109.3	113.0	112.0	105.4	C-18	-	124.6	128.7	128.1	125.2
C-7	66.3	64.0	65.1	62.5	64.8	C-19	-	128.2	128.7	128.4	125.9
C-8	71.9	72.0	70.7	77.1	70.4	C-20	-	125.1	125.9	134.4	127.1
C-9	44.8	43.4	45.2	46.1	43.6	C-21	-	129.1	123.8	-	-
C-10	190.4	192.7	190.9	189.9	187.9	C-22	-	-	129.7	-	-
C-11	121.8	111.5	113.3	122.6	123.1	C-23	-	-	128.1	-	-
C-12	129.0	131.0	132.8	129.2	128.4	C-24	-	-	129.7	-	-

[i] In ppm from TMS
[ii] $CDCl_3$ as a solvent.
[iii] Acetone-D6 as a solvent

Table 3. ^{1}H NMR chemical shifts of rotenoids **6a-e**[i]

Atom	**6a**[ii]	**6b**[ii]	**6c**[ii]	**6d**[iii]	**6e**[ii]
H-2	6.38	7.07	-	-	-
H-4	6.38	6.43	7.34-7.37	7.72-7.84	7.46-7.49
H-5	7.86	7.74	7.70-7.74	7.72-7.84	7.46-7.49
H-7	4.15(α), 4.58(β)	4.34–4.40	4.32(α), 4.82(β)	4.57(α), 4.80(β)	4.40(α), 4.89(β)
H-8	4.88	5.18	5.12	5.72	5.09
H-9	3.82	4.34-4.40	4.05	4.57	4.12
H-12	7.09	-	-	7.35-7.50	8.04
H-13	6.86-7.04	-	-	7.01	-
H-14	7.09	7.72	7.52-7.60	7.35-7.50	7.25
H-15	6.86-7.04	7.07	7.34-7.37	7.01	6.83
H-17	3.65	3.72	8.21	8.20	8.19
H-18	-	9.13	7.34-7.37	7.35-7.50	7.34
H-19	-	7.59	7.34-7.37	7.35-7.50	7.71
H-20	-	7.40	7.70-7.74	8.09	7.46-7.49
H-21	-	7.87	7.70-7.74	-	-
H-22	-	-	8.16	-	-
H-23	-	-	7.34-7.37	-	-
H-24	-	-	7.52-7.60	-	-

[i] In ppm from TMS.
[ii] $CDCl_3$ as a solvent.
[iii] Acetone-D6 as a solvent.

Table 4. ^{1}H-^{1}H coupling constants (Hz) for rotenoids **6a-e**

Coupling constant	Pair of protons	**6a**	**6b**	**6c**	**6d**	**6e**
^{2}J	7α-7β	12.0	-	12.0	-	12.0
^{3}J	7β-8	3.0	-	4.0	-	4.0
	4-5	9.2	8.2	-	-	-
	8-9	3.5	-	4.0	-	4.0
	14-15	-	8.2	-	-	8.7
	12-13	9.2	-	-	-	-
	20-21	-	9.0	-	-	-
	17-18	-	-	8.7	-	-
	18-19	-	8.5	-	-	-
^{4}J	12-14	-	-	-	-	2.5