Four New Clerodane Diterpenoids from Callicarpa pentandra

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Four New Clerodane Diterpenoids from *Callicarpa pentandra*

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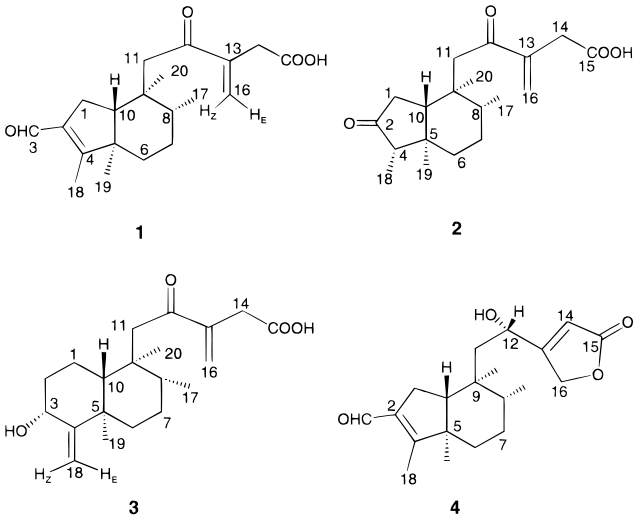
Leaf extracts of *Callicarpa pentandra* provided four new clerodane-type diterpenoids (**1**−**4**), of which **1**, **2**, and **4** have ring-A-contracted structures. Their structures and stereochemistry were established by spectral data interpretation, and for **3** also by single-crystal X-ray diffraction.

Plants of the genus *Callicarpa* are known to have medicinal properties, for example, for the treatment of rheumatism, stomach disorders, and intestinal troubles.[1] Studies on piscicidal constituents have also been reported.[2,3] The Malaysian species *Callicarpa pentandra* Roxb. (Verbenaceae), as a liquid is drunk for colds in folk medicine.[4] We now report the isolation and structural elucidation of four clerodane diterpenoids (**1**−**4**; pentandranoic acids A−C and pentandralactone), three of which have a new contracted ring-A clerodane skeleton.



Results and Discussion

Pentandranoic acid A (**1**) was determined to have the molecular formula $C_{20}H_{28}O_4$ by HREIMS, with major fragment peaks at *m/z* 204 $[C_{14}H_{20}O]^+$, 189 $[C_{13}H_{17}O]^+$, and 161 $[C_{12}H_{17}]^+$. The IR spectrum was consistent with the presence of an α,*β*-unsaturated aldehyde (1659 cm^{-1}), a carboxylic acid function (1710 cm^{-1}), and an α,*β*-unsaturated ketone (1682 cm^{-1}). The ^1H NMR spectrum showed an aldehydic proton at δ_H 9.90 (Table 1), which correlated (HMQC) with the absorption at δ_C 188.9 (Table 2), and thus verified the presence of the α,*β*-unsaturated aldehyde function. This was also confirmed by a HMBC experiment showing H-3 correlating with C-1 (^3J) and C-2 (^2J) (Table 3). The ^1H NMR spectrum also exhibited vinylidene protons at δ_H 6.13 and 5.90, which were found to be attached to C-16 (δ_C 126.9) from the HMQC experiment, and they showed long-range correlations with C-12 (^3J) and C-13 (^2J) (δ_C 200.8 and 143.2, respectively) in the HMBC spectrum. Thus, another α,*β*-unsaturated ketone could be assumed. A weak carbon signal at δ_C 174.5 (C-15), which showed a ^2J interaction with δ_H 3.29 (H_2-14), was assigned to a carboxylic acid. The H_2-14 signal also exhibited HMBC interactions with C-12, C-13, and C-16. Finally, the positions of the four methyl groups were determined by the HMBC experiment (see Table 3), for example, Me-18 had correlations with C-2, C-4, and C-5 and Me-20 with C-8, C-9, C-10, and C-11. Thus, from NMR spectroscopy the structure of compound **1** could be deduced as an A-norclerodane derivative. Comparison of the ^1H and ^{13}C NMR data with those reported[5,6] allowed the confirmation of structure **1** as a modified clerodane skeleton. In the NOESY experiment, H-10 showed correlations with H_β-1, H_β-6, and H-8, whereas Me-19 had cross-peaks with H_α-1 and H_α-6. Moreover, Me-17 and Me-19 showed correlations with each other (see Table 3). Thus, the stereochemical relationships for the methyl groups and H-10 were assigned as 17α, 19α, 20α, and 10*β*, and compound **1** could be determined as 2-formyl-12-oxo-A-norcleroda-2,13(16)-dien-15-oic acid. Noteworthy is that a contraction of ring A in the clerodane structure is rare.[6]

Pentandranoic acid B (**2**) was isolated from the same fraction as **1**, and a norditerpene skeleton was indicated by HREIMS with the formula $C_{19}H_{28}O_4$, which had one carbon less than **1** and the absence of a formyl group. In support of this, the main MS fragment peak was at *m/z* 192 ($C_{13}H_{20}O$) instead of the base peak at *m/z* 204 ($C_{14}H_{20}O$) for compound **1**. The ^{13}C NMR spectrum (Table 2) indicated that C-2 was a carbonyl carbon, showing long-range correlations with H-1, H-4, H-10, and Me-18 in the HMBC spectrum. In turn, Me-18 had long-range couplings with C-2, C-4, and C-5. The α-configuration of Me-20 was determined by NOESY correlations with H-18 and H-19. Furthermore, the fact that H_β-6 correlated with H-10, while H_α-6 showed a cross-peak with Me-19, indicated that H-10 and Me-19 are transoid. Compound **2** could also be named as 2,12-dioxo-A-norclerod-13(16)-en-15-oic acid.

Pentandranoic acid C (**3**), the most polar of the four compounds, had the formula $C_{20}H_{30}O_4$, as determined by HREIMS. A comparison of its ^1H and ^{13}C NMR spectral data with those of compounds **1** and **2** suggested that the structure of **3** was similar except for the presence of two fused six-membered rings. HMQC and HMBC experiments confirmed the clerodane skeleton.[7] However, in compound **3**, one more vinylidene carbon was present at position C-18 (δ_H 4.83, 4.78; δ_C 109.8). The much deshielded nature of H-3 (δ_H 4.30) and C-3 (δ_C 74.6) indicated the presence of a hydroxyl group, and its α configuration was determined by the NOESY spectrum and confirmed by single-crystal X-ray analysis (Figure 1). Thus, compound **3**, named as 3α-

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Table 1. ^{1}H NMR (500 MHz) Spectral Data of **1**−**4** in $CDCl_3$

H	1	2	3	4	4[a]
1α	2.15 (ddq, 14.0, 10.0, 0.8)	1.98 (dd, 17.5, 13.5)	1.47 (qd, 12.1, 3.3)	2.15 (ddq, 14.2, 12.1, 0.9)	2.22 (ddq, 14.2, 11.9, 1.0)
1*β*	2.3 (dd, 14.0, 5.7)	2.22 (dd, 17.5, 7.0)	1.81 (ddt 12.1, 2.0, 3.3)	2.49 (dd, 14.2, 6.0)	2.76 (dd, 14.2, 6.0)
2α			1.92 (ddt, 13.5, 3.0, 3.3)		
2*β*			1.53 (dddd, 13.5, 12.1, 3.3, 3.0)		
3	9.90 (s)		4.30 (t, 3.0)	9.89 (s)	10.0 (s)
4		1.94 (q, 7.0)			
6α	1.62 (dt, 12.0, 3.5)	1.68 (dt, 12.5, 3.2)	1.65 (dt, 12.2, 3.0)	1.63 (dt, 12.1, 3.3)	1.40 (dt, 12.7, 3.7)
6*β*	1.44 (ddd, 12.0, 8.5, 5.0)	1.34 (dt, 12.5, 5.0)	1.46 (m)	1.34 (dt, 12.1, 4.7)	1.23 (dt, 12.7, 5.3)
7	1.53 (2 H, m)	1.49 (2 H, m)	1.44 (2 H, m)	1.55 (2 H, m)	1.44 (2 H, m)
8	1.89 (m)	1.90 (m)	1.88 (m)	1.51 (m)	1.30 (m)
10	2.04 (dd, 10.0, 5.7)	2.12 (dd, 13.5, 7.0)	1.57 (dd, 12.1, 2.0)	1.81 (dd, 12.1, 6.0)	1.78 (dd, 11.9, 6.0)
11a	2.70 (2 H, s)	2.55 (d, 15.6)	2.64 (d, 16.0)	1.44 (dd, 15.3, 2.1)	1.03 (dd, 15.3, 1.8)
11b		2.73 (d, 15.6)	2.81 (d, 16.0)	1.79 (dd, 15.3, 8.6)	1.56 (dd, 15.3, 9.4)
12				4.76 (dd, 8.6, 2.1)	4.20 (dd, 9.4, 1.8)[b]
14a	3.29 (2 H, s)	3.23 (d, 16.5)	3.25 (d, 16.5)	5.88 (d, 1.3)	5.73 (d, 1.3)
14b		3.28 (d, 16.5)	3.30 (d, 16.5)		
16*Z*	6.13(br, s)	6.10 (br, s)	6.14 (br, s)	4.82 (2 H, d, 1.3)	4.33 (2 H, d, 1.3)
16*E*	5.90 (br, s)	5.88 (br, s)	5.88 (br, s)		
17	0.84 (3 H, d, 6.8)	0.89 (3 H, d, 6.7)	0.85 (3 H, d, 6.8)	0.78 (3 H, d, 6.2)	0.70 (3 H, d, 6.7)
18	2.00 (3 H, d, 0.8)	0.86 (3 H, d, 7.0)	4.83 *Z* (br, s)	1.97 (3 H, d, 0.9)	1.62 (3 H, d, 1.0)
			4.78 *E* (br, s)		
19	0.91 (3 H, s)	0.72 (3 H, s)	1.22 (3 H, s)	0.88 (3 H, s)	0.76 (3 H, s)
20	0.97 (3 H, s)	0.92 (3 H, s)	0.84 (3 H, s)	0.88 (3 H, s)	0.80 (3 H, s)

[a] Measured in benzene-d_6. [b] δ = 5.00 in pyridine-d_5.

Table 2. ^{13}C NMR (125 MHz) Spectral Data of **1**−**4** in $CDCl_3$

C	1	2	3	4[a]
1	26.8	35.9	17.8	27.3
2	137.2	219.4	34.1	137.6
3	188.9		74.6	187.7
4	172.0	59.4	160.1	169.5
5	50.8	42.7	39.9	50.8
6	33.7	37.7	37.5	34.0
7	28.3	27.8	27.0	28.5
8	38.0	38.0	36.8	38.3
9	40.2	39.8	42.3	38.8
10	53.7	49.7	48.0	55.5
11	44.9	44.8	43.1	46.0
12	200.8	200.6	201.0	65.5
13	143.2	143.1	143.2	173.2
14	37.4	37.0	37.2	114.5
15	174.5	174.5	175.7	172.9
16	126.9	127.2	126.7	70.2
17	15.8	15.9	16.6	15.4
18	9.7	17.1	109.8	9.0
19	17.0	14.2	22.8	16.9
20	17.7	17.0	17.8	17.2

[a] Measured in benzene-d_6.

hydroxy-12-oxo-cleroda-4(18),13(16)-dien-15-oic acid, has the structure shown, and NMR data are given in Tables 1, 2, and 3.

Pentandralactone (**4**), with the molecular formula $C_{20}H_{28}O_4$ determined by HREIMS, had a 2-formyl-A-norclerodane structure, as in **1**. However, the side chain carried an α,*β*-unsaturated *γ*-lactone whose ^{1}H and ^{13}C NMR spectral data were consistent with those of similar compounds having this feature.[8−10] In addition, in the HMBC experiment, H-14 was observed to have correlations with C-13 (^2J), C-15 (^2J), and C-16 (^3J) and H-16 with C-13 (^2J), C-14 (^3J), and C-15 (^3J). The chemical shift of C-16 (δ_C 70.2) indicated it is an oxgenated methylene. Another hydroxyl group was assigned at C-12 according to the NMR signals observed (δ_H 4.74, δ_C 65.5). The assignment of H-12 was confirmed by the long-range correlations with C-11, C-13, C-14, and C-16. The absolute configuration of C-12 was assigned *S* by comparison of its ^{1}H and ^{13}C NMR spectra data with those reported for related diastereomeric compounds,[8−10] in particular, the NOESY H-8 to H-12

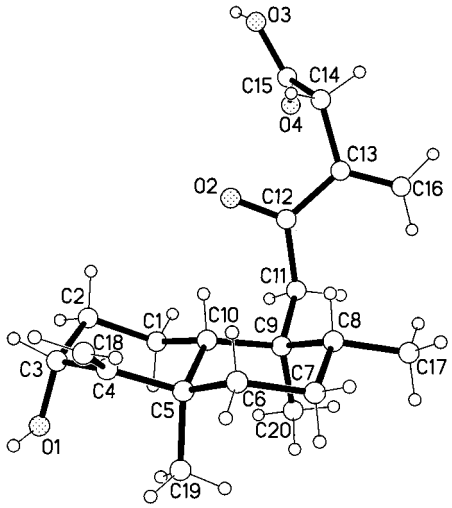

Figure 1. X-ray structure of **3**.

correlation.[11] This pentandralactone also could be named as 2-formyl-12*S*-hydroxy-A-norcleroda-2,13(14)-dien-15,16-olide.

The known compounds ursolic, corosolic, and pomolic acids, as well as 2α,3α-dihydroxyurs-12-en-28-oic acid, were also isolated from *C. pentandra* leaves, and their structures were determined by comparison of their ^{1}H NMR, ^{13}C NMR, and MS data with reported values.[12]

Experimental Section

General Experimental Procedures. Melting points were recorded on a GALEN III hot-stage microscope and are uncorrected. Optical rotations at 25 °C were taken on a DIP-1000 polarimeter. UV spectra were recorded on a Hewlett-Packard 8452A diode array spectrometer, and IR spectra were measured on a Bio-Rad FT-IR spectrometer. NMR spectra were recorded by a Bruker AMX 500 [500 MHz (^{1}H) and 125 MHz (^{13}C)] instrument (with standard pulse programs from Bruker pulse sequences library) in $CDCl_3$ solutions (unless otherwise specified) with TMS as an internal standard. EIMS were obtained on a Micromass VG 7035 mass spectrometer at 70 eV.

Liquid chromatography was carried out using Kieselgel 60 Si gel (230−400 mesh, Merck), Sephadex LH-20, Lichroprep

Table 3. Selected HMBC and NOESY Spectral Data of **1**−**4** in $CDCl_3$

position	**1**		**2**		**3**		**4**	
H[a]	HMBC[b]	NOESY[a]	HMBC[b]	NOESY[a]	HMBC[b]	NOESY[a]	HMBC[b]	NOESY[a]
1α	2, 10	19, 20			5		2	19, 20
1*β*	2, 4, 5, 10	10	2, 5, 9, 10	4	2		2, 5	10
2α					1, 3, 4, 10			
3	1, 2	18			1, 5, 18	2α, 2*β*, 18*Z*	1, 2	
4			2, 5, 6, 18, 19	6*β*, 18				
6α	5, 7, 8, 10, 19	19	5,7, 8, 10	19	5, 8, 10		8, 10	
6*β*	5, 7, 19		4, 5, 7, 19		5, 10			
7	6, 8	17, 19, 20	5, 8, 9	17, 19, 20	9		5, 8	6*β*, 11a, 19
8	9, 17, 20	17	7, 9, 17, 20	6*β*, 7, 10		17		
10	1, 5, 9, 19, 20	6*β*, 8	1, 2, 5, 9, 11, 19	1*β*, 4, 6*β*	1, 5, 9, 19, 20	1*β*,[c] 6*β*[c]	19, 20	6*β*, 8
11a	8, 9, 10, 12, 20	17, 20	8, 9, 10, 12, 20		8, 9, 10, 12, 20		9, 10, 20	
11b		1*β*, 8, 10	8, 9, 10, 12, 20	16*Z*, 17, 20	8, 9, 10, 12, 20	1α, 20	8, 12	
12							11, 13, 14, 16	8
14	12, 13, 15, 16	16 *E*	12, 13, 16	16*E*	12, 13, 15, 16		13, 15, 16	
16*Z*	12, 14	11	12, 13		12, 13, 14	11a	13, 14	
16*E*	13	8	12, 13			14a, 14b	15	
17	7, 8, 9		7, 8, 9	19	7		7, 8, 9	
18	2, 4, 5	19	2, 4, 5		3, 5		2, 4, 5	
18[d]					3, 5	6α, 6*β*		
19	4, 5, 6, 10		4, 5, 6, 10		4, 5, 6, 10	1α, 6α, 7, 17	4, 5, 6	
20	8, 9, 10, 11	17	8, 9, 10, 11	18, 19	8, 9, 10, 11	1α, 19	8, 9, 10, 11	

[a] Numbers for protons are as in Table 1. [b] Numbers refer to carbons. [c] Weak signals. [d] Refers only to 18*E* in compound **3**.

RP_{18} (40−63 μm, Merck), and Lichroprep Diol (25−40 μm, Merck). TLC was carried out on Si gel precoated glass plates (Merck, Kieselgel $60F_{254}$, 250 μm), C_{18} plates (Whatman, $KC_{18}F$, 200 μm), and Diol Si gel precoated plates (Merck, HPTLC−Fertigplatten Diol $F_{254}S$, 200 μm).

Plant Material. The leaves of *C. pentandra* were collected in Kinabatangan, Sabah, Malaysia, in June 1997. A voucher specimen (SAN135275) has been deposited at the herbarium of the Forest Research Centre, Sepilok, Sandakan, Sabah, Malaysia.

Extraction and Isolation. The air-dried and powdered leaves (910 g) of *C. pentandra* were extracted exhaustively with MeOH (20 L) and then CH_2Cl_2−MeOH (1:1). Evaporation in vacuo provided a residue that was suspended in 10% methanol in water, then extracted with *n*-hexane, $CHCl_3$ and *n*-BuOH, consecutively. The $CHCl_3$ fraction (70 g) was chromatographed initially over Si gel with solvent gradients using hexane, $CHCl_3$, and MeOH and provided two major fractions (I and II). Fraction I (about 20 g) was eluted by hexane−$CHCl_3$ (1:1) to pure $CHCl_3$ and fraction II (13 g) from pure $CHCl_3$ to MeOH−$CHCl_3$ (1:9). Ursolic acid (560 mg) was isolated from fraction I after chromatography on Sephadex LH-20 eluting with $CHCl_3$−MeOH (1:1). This fraction also gave corosolic acid (6.0 mg) after flash column chromatography on Si gel and a Diol column eluting with MeOH−$CHCl_3$ (1:99). Two other known compounds, pomolic acid (30 mg) and 2α,3α-dihydroxyurs-12-en-28-oic acid (1.3 mg), were obtained from fraction II after repeated chromatography on Si gel eluting with MeOH−$CHCl_3$ (3:97). The new clerodane diterpenoids **1**−**4** were isolated from fraction II by flash chromatography (twice) on Si gel (1−3% MeOH in $CHCl_3$), followed by passage over a RP_{18} reversed-phase column (MeOH−H_2O, 3:2) and a Diol column ($CHCl_3$). Further purification of compounds **1** and **2** was carried out by preparative TLC (Si gel) with Me_2CO−EtOAc−hexane (1:2:8) to obtain **1** (8.6 mg, R_f 0.25) and **2** (3.1 mg, R_f 0.30). Compound **3** (17.1 mg) was purified by Si gel preparative TLC with Me_2CO−EtOAc−hexane (1:2:8, R_f 0.20); **4** (2.6 mg) was similarly purified eluting with EtOAc−hexane−HOAc (3:7:0.05, R_f 0.25).

Pentandranoic acid A [2-formyl-12-oxo-A-norcleroda-2,13(16)-dien-15-oic acid] (1): colorless viscous solid (8.6 mg); $[\alpha]_D$ +44.9° (*c* 0.86, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 268 (2.98), 276 (2.74) nm; IR (KBr) ν_{max} 3024, 2961, 2930, 2860, 2750, 1710 (CO_2H), 1682 (C═C−C═O), 1659 (CHO), 1612 (C═C) cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m*/*z* 332 (M^+, 18), 317 ($M^+ - CH_3$, 39), 204 ($C_{14}H_{20}O^+$, 92), 189 ($C_{13}H_{17}O^+$, 100), 161 ($C_{12}H_{17}^+$, 98); HREIMS *m*/*z* M^+ 332.1976 (calcd for $C_{20}H_{28}O_4$, 332.1988).

Pentandranoic acid B [2,12-dioxo-A-norclerod-13(16)-en-15-oic acid] (2): colorless viscous solid (3.1 mg); $[\alpha]_D$ +94.2° (*c* 0.31, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 242 (2.68) nm; IR (KBr) ν_{max} 3023, 2967, 2930, 1729 (CO), 1716 (CO_2H), 1684 (C═C−C═O) cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m*/*z* 320 (M^+, 8), 302 ($M^+ - H_2O$, 8), 192 ($C_{13}H_{20}O^+$, 100), 177 ($C_{12}H_{17}O^+$, 75), 121 (70), 69 (67), 41 (68); HREIMS *m*/*z* M^+ 320.2010 (calcd for $C_{19}H_{28}O_4$, 320.1988).

Pentandranoic acid C [3α-hydroxy-12-oxo-cleroda-4(18),13(16)-dien-15-oic acid] (3): colorless crystals (17.1 mg); mp 135−137 °C; $[\alpha]_D$ +15.2° (*c* 0.86, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 242 (2.69) nm; IR (KBr) ν_{max} 3093 (OH, br), 3018, 2961, 2930, 1715 (CO_2H), 1682 (C═C−C═O), 1630 (C═CH_2) cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m*/*z* 334 (M^+, 6), 316 ($M^+ - H_2O$, 12), 301 ($M^+ - H_2O - CH_3$, 14), 206 ($C_{14}H_{22}O^+$, 92), 173 (100), 118 (100), 55 (90); HREIMS *m*/*z* M^+ 334.2131 (calcd for $C_{20}H_{30}O_4$, 334.2144).

Crystal Data for Compound 3: $C_{20}H_{30}O_4$, M = 334.44, monoclinic, $P2_12_12_1$, a = 7.2303(1), b = 11.5201(3), c = 22.5240-(5) Å, V = 1876.11(7) Å^3, Z = 4, μ(Mo *K*α) = 0.081 mm^{-1}, 9288 reflections measured, 3280 unique (R_{int} = 0.0272), final R_1, wR_2, and GOF values are 0.045, 0.0970, and 1.099 for 2771 independent reflections [$I \geq 2\sigma(I)$] and 265 parameters. In the final difference Fourier synthesis, the electron density fluctuates in the range 0.248 to −0.138 e Å^{-3}. The data collection was performed at 295 K on a Bruker SMART CCD area-detector by ω-scan method, within the limits 1.8° ≤ θ ≤ 25.0°. The data were corrected for absorption using an empirical method (SADABS), and the structure was solved by direct methods and refined by full-matrix least-squares (SHELXTL) on F^2. Crystallographic data for **3** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-(0)1223-336033 or E-mail: deposit@ccdc.cam.ac.uk].

Pentandralactone [2-formyl-12*S*-hydroxy-A-norcleroda-2,13(14)-dien-15,16-olide] (4): colorless solid (2.6 mg); mp 53−55 °C; $[\alpha]_D$ +263.5° (*c* 0.26, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 260 (2.77), 268 (2.76) nm; IR (KBr) ν_{max} 3400 (OH, br), 3014, 2935, 2855, 2730 and 1748 (α,*β*-unsaturated γ-lactone), 1650 (CHO), 1612 (C═C) cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m*/*z* 332 (M^+, 4), 317 ($M^+ - CH_3$, 48), 205 ($C_{14}H_{21}O^+$, 46), 189 ($C_{14}H_{21}+$, 80), 107 (82), 55 (100); HREIMS *m*/*z* M^+ 332.1976 (calcd for $C_{20}H_{28}O_4$, 332.1988).

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Supporting Information Available: NMR data for compounds **1** and **4** (Tables 1 and 2) and X-ray crystallographic data (Tables 3−7) for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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