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3α-HYDROXY-LUP-20(29)-ENE-23,28-DIOIC ACID FROM *SCHEFFLERA OCTOPHYLLA**

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Key Word Index—*Schefflera octophylla*; Araliaceae; triterpenes; 3α-hydroxy-lup-20(29)-ene-23,28-dioic acid.

Abstract—The main triterpene from leaves of *Schefflera octophylla* was isolated in a high yield (7%) and its structure determined as 3α-hydroxy-lup-20(29)-ene-23,28-dioic acid by physical data and chemical transformations.

INTRODUCTION

Although the occurrence of triterpene saponins is described as typical for the Araliaceae family [1] there seem to be no investigations on such constituents in the genus *Schefflera* [2]. Continuing a programme of studies on Vietnamese plants of medical and biological interest, we have examined the species *Schefflera octophylla* (Araliaceae) which is used in Vietnamese folk medicine [3] as a tonic drug, an antirheumatic agent and for liver diseases. We now report the isolation of a new pentacyclic triterpene isolated from dried leaves of this plant in a very high yield of 7%. Based on spectroscopic data and chemical transformations the structure of this constituent is shown to be 3α-hydroxy-lup-20(29)-ene-23,28-dioic acid (**1**).

RESULTS AND DISCUSSION

Extraction of dried leaves of the plant with petrol followed by EtOH–H_2O (1:1) and evaporation of the latter extract yielded a crystalline compound $C_{30}H_{46}O_5$ (**1**) ($[M]^+$ at *m/z* 486.3363, calc. 486.3345) with IR absorptions (nujol) at 1640 and 3075 ($\rangle C{=}CH_2$), 1705 and 2725 (COOH) as well as at 3300 cm^{-1} (OH). The formation of the dimethyl ester **2** and a monoacetyl derivative **3** indicated the presence of two carboxylic functions and one hydroxyl. Oxidation of **2** with PCC in methylene chloride gave the keto diester **4** with a weak negative 3-carbonyl Cotton effect at 288 nm ($a = -7$) which has been observed previously for A/B *trans*-fused 3-keto-4, 4-dimethyl triterpenoids [4]. Sodium borohydride reduction of **4** yielded the 3β-epimeric diester **5**. Whereas the dimethylate **2** showed in the IR an intramolecular COOR...HO hydrogen bond ($\Delta\gamma =$ 120 cm^{-1}), such an interaction could not be observed in the 3-epimer (**5**).

The ^1H NMR spectrum of **1** showed two olefinic protons at δ 4.58 and 4.71, a one-proton triplet at 3.76 (which moved to 4.90 in the spectrum of the acetate **2**, equatorial 3β-H) and five tertiary methyl groups (one of them low-field shifted to δ 1.69). The ^{13}C NMR spectrum of **1** established the presence of two carboxylic groups (*s*, 178.1 and *s*, 177.6), one 1, 1-disubstituted double bond (*s*, 151.6 and *t*, 110.0) and a secondary hydroxyl (*d*, 72.8). The assignment of all 30 carbon atoms was achieved by comparison with the known values of betulinic acid [5] and its methylate [6] for ring E. With regard to the ring A substitution pattern the data for 29-acetoxyhopan-22-ol and methyl leucotylate were considered [6]. An observed steric compression shift for C-1 and C-5 in the dimethylate **2** in comparison to the corresponding signals of the 3β-epimer **5** [δ values found for **2**, 33.0 (C-1) and 45.1 (C-5); **5**, 39.4 (C-1) and 52.4 (C-5)] confirmed the axial α-position of the 3-hydroxyl group. By contrast, in the 3β-epimer **5**, such a highfield shift is observed for the C-24 methyl signal (δ value for **2**, 17.5; **5**, 11.3).

The fragmentation pattern in the mass spectrum of **1** showed significant ions at *m/z* 250 (*c*), 248 (*b*), 237 (*a*), 234 (*d*) and 219 (*e*) arising by the bond cleavages of ring C shown in Scheme 1. Corresponding shifts of the fragment ions *a–e* in the derivatives **2–6** (see, Experimental) confirmed the assignment of the functional groups to the A/B and C/D ring parts, respectively [7]. The *g*-type ion (*m/z* 169, $C_9H_{13}O_3$), which is also found in the mass spectrum of 3-oxo-allobetulane [8], allowed the carbonyl group and one of the carboxylic functions to be established at positions C-3 and C-4, respectively.

In the dimethyl ester **2**, ions of type f_1 and f_2 were observed and these ions are also present in the mass spectrum of betulic acid methyl ester. Their appearance suggested the position of the second carboxylic group to be at C-28.

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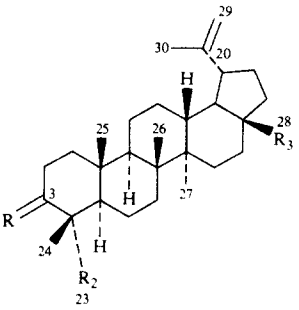
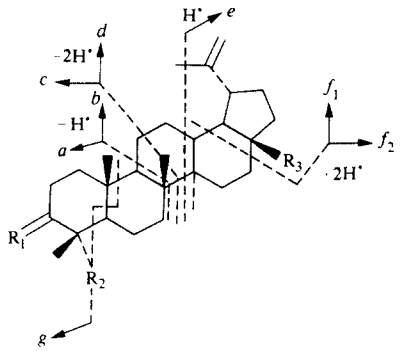


	1	2	3	4	5	6	7
R_1	α – OH; β – H	α – OH; β – H	α – OAc; β – H	O	α – H; β – OH	α – OH; β – H	α – OTs; β – H
R_2	COOH	COOMe	COOH	COOMe	COOMe	CH_2OH	CH_2OTs
R_3	COOH	COOMe	COOH	COOMe	COOMe	CH_2OH	CH_2OTs



Scheme 1. Mass spectral fragmentations of compounds **1–7**.

From these data the isolated triterpene was identified as 3α-hydroxy-lup-20(29)-ene-23,28-dioic acid (**1**). Further proof of the presence of the lupane skeleton in **1** was accomplished in the following manner. Lithium aluminium hydride reduction of the dimethylate **2** gave the triol **6** which upon transformation to the tritosylate **7** and subsequent reaction with lithium aluminium hydride afforded the known [9] lupa-2, 20(29)-diene.

EXPERIMENTAL

Mps are corr. Specific rotations in MeOH; ^{1}H NMR spectra in Me_2CO-d_6 with HMDS as int. standard; ^{13}C NMR in Me_2CO-d_6 at 50.3 MHz, δ values in ppm downfield from TMS: δ (TMS) = δ (Me_2CO-d_6) + 29.8 ppm; ORD in MeOH; low resolution MS at 10–16 eV; high resolution MS at 75 eV. *Schefflera octophylla* (Lour.) Harms was identified by Dr. Ph. V. Nguyen, Institute of Biology, National Research Centre of the SRV, Hanoi, and a voucher specimen is kept there.

Isolation of 3α-hydroxy-lup-20(29)-ene-23,28-dioic acid (**1**). Dried and powdered leaves (100 g), collected near Hanoi, were extracted with petrol in a Soxhlet and subsequently with EtOH–H_2O (1:1) for 4 hr under reflux. Evaporation of the solvent from the filtered extract yielded **1** (7 g): Compact crystals (Me_2CO–*n*-hexane), mp 260–262°, $[\alpha]_D^{25}$ – 10.9° (*c* 0.43). MS 10–16 eV *m/z* (rel. int.): 486 $[M]^+$ (15), 468 (10), 440 (32), 424 (23), 302 (16), 259 (60), 250 (57, *c*), 248 (70, *b*), 237 (46, *a*), 234 (74, *d*), 219 (77, *e*), 215 (50), 203 (81), 189 (100), 175 (98), 161 (80), 152 (34, f_1), 147 (82), 133 (83), 121 (88), 107 (83); ^{1}H NMR: δ 0.89, 0.95, 1.04, 1.14 (4 × *s*, 24-H_3, 25-H_3, 26-H_3, 27-H_3), 1.69 (*s*, 30-H_3), 3.76 (*t*, $J_{AX} + J_{BX}$ = 5.4 Hz, 3β-H), 4.58 and 4.71 (2 × *m*, 29-H_2). Further spectral data in the text.

Dimethyl ester **2**. Obtained from **1** by treatment with CH_2N_2 in MeOH. Amorphous; $[\alpha]_D^{25}$ – 12.0° (*c*0.39); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640 (>C=CH_2), 1730 (COOMe), 3070 (>C=CH_2), 3500 (*br* OH); concn 2 mmol/l. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3510 (*br* COOMe .... HO), 3630 (free OH); MS *m/z* (rel. int.): 514 $[M]^+$ (21), 482 (13), 454 (15), 423 (10), 316 (9), 273 (39), 264 (63, *c*), 262 (73, *b*), 251 (58, *a*), 249 (87, *d*-H), 233 (76, *e*), 215 (41), 203 (84), 189 (100), 175 (91), 168 (37, f_2), 166 (36, f_1), 161 (55), 147 (60), 133 (60), 119 (65), 107 (57); ^{1}H NMR: δ 0.88, 0.93, 1.04, 1.12 (4 × *s*, 24-H_3, 25-H_3, 26-H_3, 27-H_3), 1.69 (*s*, 30-H_3), 3.57 and 3.64 (2 × *s*, COOMe), 3.70 (*t*, $J_{AX} + J_{BX}$ = 5.4 Hz, 3β-H), 4.59 and 4.71 (2 × *m*, 29-H_2).

Acetate **3**. Obtained from **1** by treatment with Ac_2O–pyridine for 16 hr at 20°: mp 207–210° (Me_2CO–*n*-hexane); $[\alpha]_D^{25}$ – 17.9° (*c*0.42); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1240 (OAc), 1640 (>C=CH_2), 1705 (COOH), 1730 (OAc), 3070 (>C=CH_2); MS *m/z* (rel. int.): 528 $[M]^+$ (8), 482 (13), 468 (14), 450 (9), 424 (50), 409 (25), 379 (16), 366 (19), 327 (14), 259 (86), 248 (70, *b*), 234 (67, *d*), 219 (79, *e*), 203 (78), 189 (94), 175 (100), 161 (75), 147 (68), 133 (60), 121 (83), 107 (82); ^{1}H NMR: δ 0.92, 0.97, 1.06, 1.21 (4 × *s*, 24-H_3, 25-H_3, 26-H_3, 27-H_3), 1.70 (*s*, 30-H_3), 1.92 (*s*, OAc), 4.58 and 4.71 (2 × *m*, 29-H_2), 4.90 (*t*, $J_{AX} + J_{BX}$ = 5.4 Hz, 3β-H).

Oxidation of **2** *to ketone* **4**. To PCC (133.5 mg) in dry CH_2Cl_2 (3 ml) compound **2** (106 mg) was added and the soln stirred at 20° for 3 hr. Standard work-up followed by CC over Si gel (elution with *n*-hexane–$CHCl_3$, 8:2) gave the ketone **4** (66 mg): mp 130–132° (*n*-hexane); $[\alpha]_D^{25}$ + 5.7° (*c*0.35); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (>C=CH_2), 1710 (C=O), 1730 (COOMe); MS *m/z* (rel. int.): 512 $[M]^+$ (64), 453 (47), 452 (44), 430 (43), 398 (33), 315 (7), 273 (36), 262 (82, *b*), 249 (94, *d*-H), 235 (24), 233 (44, *e*), 217 (50), 203 (80), 189 (100), 175 (76), 169 (51, *g*), 168 (41, f_2), 166 (32, f_1), 161 (42), 147 (48), 133 (60), 119 (65), 107 (50); ^{1}H NMR: δ 0.97, 1.03, 1.03, 1.28 (4 × *xs*, 24-H_3, 25-H_3, 26-H_3, 27-H_3), 1.69 (*s*, 30-H_3), 3.63 and 3.64 (2 × *s*, COOMe), 4.59 and 4.72 (2 × *m*, 29-H_2).

Reduction of **4** *to 3β-alcohol* **5**. To a soln of **4** (50 mg) in 5 ml MeOH–THF (1:1) was added $NaBH_4$ (40 mg) and the

mixture stirred at 20° for 0.5 hr. The excess $NaBH_4$ was decomposed with dil. HOAc and the solvent evaporated. The product was passed through a Si gel column (elution with *n*-hexane–$CHCl_3$, 6:4) to afford **5** (40 mg): mp 232–233° (Et_2O–*n*-hexane); $[\alpha]_D^{25}$ + 19.0° (*c*0.30); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640 (>C=CH_2), 1725 (COOMe), 3075 (>C=CH_2), 3500 (*br* OH); concn 2 mmol/l. $\nu_{max}^{CCl_4}$ cm^{-1}: 3630 (free OH); MS *m/z* (rel. int.): 514 $[M]^+$ (35), 482 (7), 454 (24), 432 (8), 395 (9), 273 (22), 264 (40, *c*), 262 (70, *b*), 251 (55, *a*), 249 (60, *d*-H), 233 (54, *e*), 203 (63), 189 (100), 175 (77), 168 (30, f_2), 167 (32, f_1 + *H*), 161 (50), 147 (58), 133 (67), 119 (77), 105 (73). ^1H NMR: δ 0.86, 0.90, 1.00, 1.07 (4 × *s*, 24-H_3, 25-H_3, 26-H_3, 27-H_3), 1.69 (*s*, 30-H_3), 3.61 and 3.64 (2 × *s*, COOMe), 3.93 (*dd*, $J_{AX} + J_{BX}$ = 15.8 Hz, 3α-H), 4.60 and 4.73 (2 × *m*, 29-H_2).

Reduction of **2** *to triol* **6**. To $LiAlH_4$ (150 mg) in dry THF (5 ml) was added **2** (60 mg) and the mixture refluxed with stirring for 10 hr. Excess $LiAlH_4$ was destroyed with EtOAc followed by H_2O. The mixture was evaporated and the residue acidified and extracted with EtOAc. The dried solvent was evaporated and the residue chromatographed over Si gel to give the triol **6** (38 mg): Amorphous $[\alpha]_D^{25}$ – 4.6° (*c*0.37); IR ν_{max}^{nujol} cm^{-1}: 1640 (>C=CH_2), 3420 (*br* OH); MS *m/z* (rel. int.): 458 $[M]^+$ (42), 440 (35), 428 (38), 427 (37), 410 (50), 409 (45), 391 (22), 379 (23), 257 (39), 245 (56), 234 (54, *b* and *c*), 223 (52, *a*), 220 (56, *d*), 205 (93, *e* and *a* H_2O), 203 (92), 189 (100), 187 (99), 175 (100), 161 (86), 147 (90), 133 (91), 121 (94), 107 (92). ^1H NMR: δ 0.67, 0.88, 1.03, 1.06 (4 × *s*, 24-H_3, 25-H_3, 26-H_3, 27-H_3), 1.68 (*s*, 30-H_3), 3.28 and 3.30 (2 × *d*, *J* = 11 Hz, 28-CH_2OH), 3.58 (*t*, $J_{AX} + J_{BX}$ = 5.4 Hz, 3β-H), 3.72 and 3.74 (2 × *d*, *J* = 11 Hz, 23-CH_2OH), 4.56 and 4.69 (2 × *m*, 29-H_2).

Lupa-2, 20(29)-*diene from triol* **6** *via tritosylate* **7**. Triol **6** (50 mg) was treated with toluene-*p*-sulphonyl chloride (250 mg) in dry pyridine at 0° for 2 days. Standard work-up gave the amorphous tritosylate **7** (52 mg) which showed no hydroxyl group absorption in the IR. It was refluxed with $LiAlH_4$ (600 mg) in dry THF (30 ml) for 3 days. Excess $LiAlH_4$ was destroyed with EtOAc followed by H_2O. Et_2O extraction and Si gel chromatography gave lupa-2,20(29)-diene (16 mg). Needles (petrol); mp 163–164° (lit. [9]: mp 164°). The compound was shown to be identical (IR, NMR, MS) with authentic lupa-2, 20(29)-diene obtained from lupeol with $POCl_3$–pyridine for 2 hr under reflux.

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