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Diterpenes Derived from Clerodane Skeleton from Some Compositae Plants†

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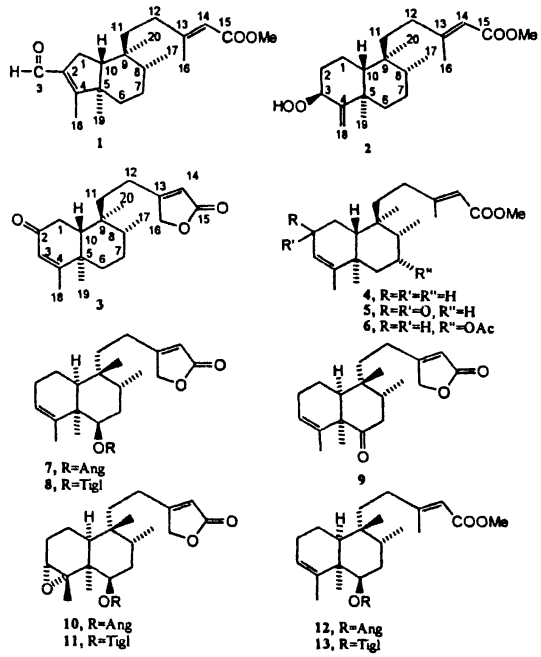
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The structures of the clerodane derivatives solidagonal acid, a diterpene with new carbon skeleton, a hydroperoxyclerodane (3β-hydroperoxy-4,18-dehydro-3,4-dihydrokolavenic acid), 2-oxo-kolavenic acid lactone, 2α-acetoxyhardwickiic acid, 10-*epi*-nidoresedic acid, 16-oxo-15,16*H*-hardwickiic acid, 15-methoxy-16-oxo-15,16*H*-hardwickiic acid, 15-methoxy-16-oxo-nidoresedic acid, *nor*-hardwickiic acid, 15-methoxy-16-oxo-15,16*H*-strictic acid, *nor*-strictic acid, 15-desmethoxy-16-oxo-15,16*H*-strictic acid, 15-oxo-14,16*H*-strictic acid, 16-oxo-14,15-epoxystrictic acid alongwith several known diterpenes, isolated from the Indian Compositae plants *Solidago altissima*, *Grangea maderaspatana* and *Pulicaria angustifolia*, have been deduced mainly from high field ^{1}H nmr, high resolution mass spectrometry and noe difference spectroscopy.

In pursuing our interest[1–3] in sesqui- and diterpenoid constituents of certain selected plants, we have chemically examined more than two dozens of Compositae and related plants which afforded a large number of sesquiterpene lactones[4–7], sesquiterpenes[8], quinones[9], polyacetylenes[10–13] and aromatic esters[14] of chemotaxonomic importance. In this short review, we present the results of structure elucidation of fourteen diterpenes specially derived from clerodane skeleton from *Solidago altissima* Linn.[15–17], *Grangea maderaspatana* Poir.[18] and *Pulicaria angustifolia* DC.[19].

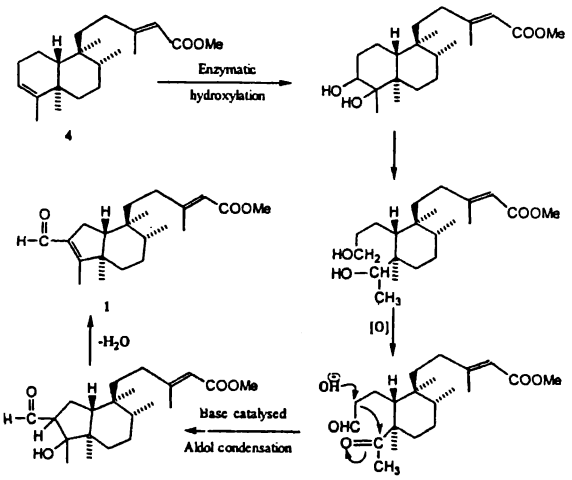
Earlier work on *S. altissima* Linn. led to the isolation of a number of *trans*-clerodane diterpenes[20–22]. Later on their stereochemistry has been revised on the basis of chemical studies by Niwa and Yamamura[23]. The clerodanes having oxygen function at C-6 position belong to the *cis*-clerodane and others having no oxygen function at the same position belong to the *trans*-clerodane series. In all cases where a C-6 oxygen function is present, the configuration is 9β-methyl and 10α-H, while in other cases 10β-H and 9α-methyl were observed. The co-occurrence of *cis*- and *trans*-clerodanes in this genus is noteworthy. During re-examination, the roots of *S. altissima* afforded a diterpene with new carbon skeleton solidagonal acid (**1**), a hydroperoxyclerodane (**2**), a ketone, 16-hydroxy-2-oxo-kolavenic-15-oic acid lactone (**3**) along with known diterpenes, viz. kolavenic acid (**4**), 2-oxo-kolavenic acid (**5**), 7α-acetoxykolavenic acid (**6**), solidagolactones-II **7**, III **8**, V **9**, VII **10**, solidagolactone tiglate (**11**), 6β-angeloyloxy- and 6β-tigloyloxy-*cis*-kolavenic acids (**12** and **13**). The aerial parts gave known solidagolactones-II **7**, III **8**, V **9**, VII **10** and the corresponding tiglate **11**.

The structure of solidagonal acid (**1**) was followed from high field ^{1}H nmr and rigorous spin decoupling experiments. It was converted into its methyl ester by addition of CH_2N_2. The ^{1}H nmr spectral data indicated the presence of an aldehyde by the singlet at δ 9.96. The similarity of several signals with those of methyl kolavenoate (**4**) showed that most likely these two diterpenes are closely related. The presence of a homoallylic coupling between H-18 and H-1 required a five-membered ring, especially by careful spin decoupling all signals and their sequences could be established. Therefore, kolavenic acid is the precursor of **1**,which may be formed via oxidative cleavage followed by aldol condensation (Scheme 1). Alternatively, a rearrangement of2-hydroxy-3,4-epoxykolavenic acid can be considered.



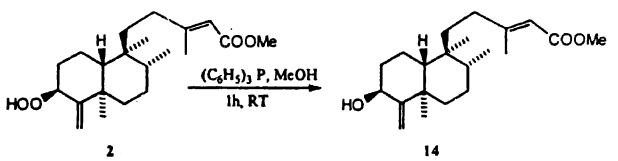
The structure of hydroperoxyclerodane (**2**) was deduced from high resolution mass and extensive spin decoupling experiments. The presence of a hydroperoxy group was indicated by the characteristic low field signal at δ 8.00 in ^{1}H nmr spectrum, which was fully supported by its ir absorp-

†Dedicated to Professor Sukh Dev on the occasion of his 75th birth anniversary



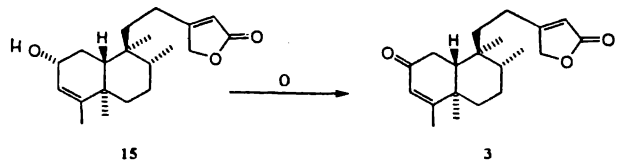
Scheme 1. Biogenetic pathway for the formation of solidagonal acid (1).

tion at 3520 cm^{-1}. The presence of hydroperoxy group was confirmed by its reduction to an alcohol **14** by treating its methanolic solution with triphenylphosphine for an hour at room temperature. The position of hydroperoxy group was followed from the broadened double doublet at δ4.60 due to H-3 which showed coupling with the vinylic protons. Its ^{1}H nmr data were comparable with those of the corresponding compounds of *trans*-kolavenic series. This compound seems to be an artefact derived from kolavenic acid through ene reaction but careful cold extraction and subsequent operations in dark ruled out the above possibility.



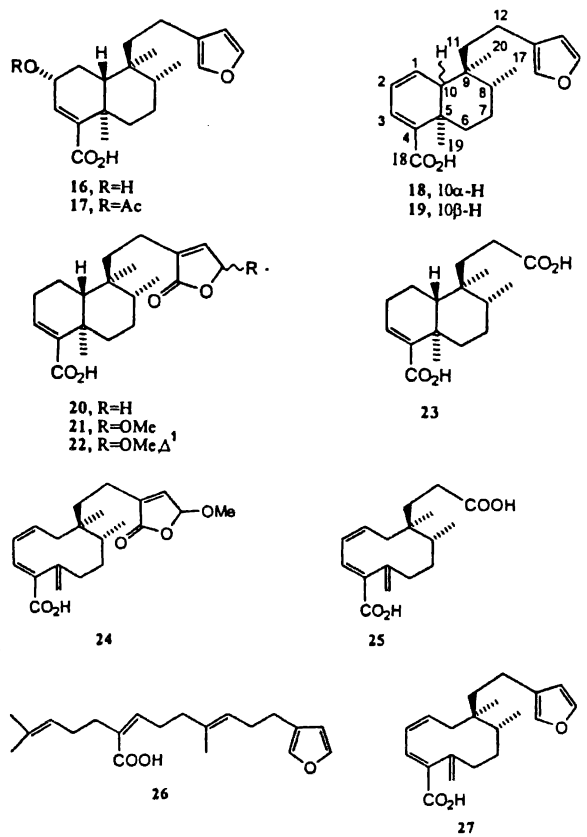
The structure of 16-hydroxy-2-oxo-kolavenic-15-oic acid lactone (**3**) was established from ^{1}H nmr and mass spectral data. A pair of widely spaced double doublets at δ2.41 and 2.26 for H-1α and H-1β protons and their large geminal coupling indicated the presence of a keto group in their vicinity. An olefinic H-3 proton appeared as broad singlet at δ5.74. A triplet quartet was observed at δ5.84 due to H-14 olefinic proton. A doublet at δ4.72 was assigned to H-16 protons attached to oxygen function. This compound was earlier reported by the oxidation of 2α,16-dihydroxy-kolavenic-15-oic acid lactone (**15**) obtained from *Symphyopappus compressus*[24]. The spectral data were in complete agreement with that of the reported one. Though this compound was synthetically known earlier, this is the first report from a natural source.

Previous work on *Grangea maderaspatana* Poir. led to



the isolation of clerodane diterpenoids[25,26]. Re-investigation of its aerial parts gave hardwickiic acid (**16**), 2α-acetoxyhardwickiic acid (**17**), 10-*epi*-nidoresedic acid (**18**), nidoresedic acid (**19**), 16-oxo-15,16*H*-hardwickiic acid (**20**),15-methoxy-16-oxo-15,16*H*-hardwickiic acid (**21**),15-methoxy-16-oxo-nidoresedic acid (**22**), *nor*-hardwickiic acid (**23**),15-methoxy-16-oxo-15,16*H*-strictic acid (**24**), *nor*-strictic acid (**25**), centipedic acid (**26**) and strictic acid (**27**). These were isolated as their methyl esters.

The structure of 2α-acetoxyhardwickiic acid (**17**) was deduced from its ^{1}H nmr spectrum which was close to that of hardwickiic acid[25] (**16**). As expected, the H-2 signal was shifted down field (δ5.42, ddd) along with the appearance of an additional acetoxy signal at δ2.08.



The ^{1}H nmr spectrum of 10-*epi*-nidoresedic acid (**18**) was similar to that of nidoresedic acid[26,27] (**19**). However, some signals were slightly different. Spin decoupling allowed the

assignment of all signals and by noe difference spectroscopy the configuration at all chiral centres could be determined. Clear effects between H-19 and H-10 (10%), H-17 and H-10 (6%), H-20 and H-17 (5%), H-10 (12%) and H-2 (7%) required a *cis*-relationship of H-10, H-17, H-19 and H-20.

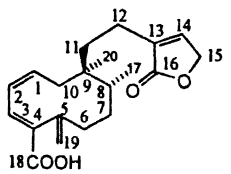
The presence of γ-lactone and conjugated acid moiety in 16-oxo-15,16*H*-hardwickiic acid (**20**) was ascertained by the appearance of strong ir absorption bands at 1770 and 1715 cm^{-1}. The ^1H nmr spectrum was very close to that of hardwickiic acid (**16**) where the side-chain furan protons were replaced by a β-substituted-γ-lactone ring. Consequently, H-14 and H-15 appeared at δ 7.09 and 4.76 as triplet of triplet and a doublet of triplet respectively. An olefinic H-3 proton β to the carbonyl function appeared more downfield (δ 6.60). The ^1H nmr spectrum of 15-methoxy-16-oxo-15,16*H*-hardwickiic acid (**21**) was close to that of **20**. However, the two-proton signal at δ 4.76 (H-15) was replaced by a broadened singlet at δ 5.75 (1H) and an additional methoxy signal at δ 3.58. The ^1H nmr spectrum of **22** indicated that again 15-methoxy derivative was present which differs from **21** by an additional 1,2-double bond. Therefore, the spectrum was in part close to that of nidoresedic acid (**19**). However, the signals of furan protons in **19** were replaced by a pair of doublet triplets at δ 6.75 and 5.74 (J 1.5, 1.5 Hz each) along with a methoxy signal at δ 3.57. Sequence and multiplicity of protons were determined by spin decoupling experiments.

The ^1H nmr spectrum of **23** was in part close to that of hardwickiic acid (**16**). Two carbomethoxy signals (1730, 1710 cm^{-1}) and molecular formula ($C_{19}H_{30}O_4$) required the presence of a *nor*-clerodane skeleton. The complete absence of signals of furan protons and the fragmentation pattern (strong peak at *m/z* 235 $[M\text{-}CH_2\text{-}CH_2\text{-}COO\ Me]^+$ in the mass spectrum) showed that a methyl propionate side-chain is at C-9.

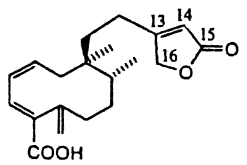
The ^1H nmr spectrum of **24** showed it to be a corresponding 15,16-butenolide of strictic acid[19,25] (**27**). Accordingly, the resonance signals of furan ring were replaced by a pair of broad singlets at δ 6.77 (H-14) and 5.74 (H-15) along with a methoxy signal at δ 3.69. The signal of H-3 proton at δ 7.25 was partly overlapped by $CDCl_3$ signal. Rest of the signals were almost identical with those of strictic acid (**27**). The ^1H nmr spectrum of **25** was very similar to that of strictic acid (**27**) barring the signals of furan protons. A loss of fragment $-CH_2-CH_2-COOMe$ from *m/z* 288 in mass spectrum suggested that a methyl propionate chain must be present in the molecule. Molecular formula together with two carbomethoxy signals required the presence of a *nor-seco*-clerodane skeleton. A pair of broad singlets at δ 5.06 and 4.84 was attributed to H-19 exomethylene protons. H-1, H-2 and H-3 olefinic protons appeared at δ 5.35, 5.93 and 7.25 respectively.

In fact strictic acid (**27**) was isolated by three separate group of workers under different names. The substance, first isolated from *Conyza stricta* Wild.[28] was named as conyzic acid. Bohlmann and Fritz[27] reported it as *seco*-nidoresedic acid from *Nidorella resedifolia*, and Tandon and Rastogi[29] isolated it from *Conyza stricta* and called strictic acid. Later on Mahato *et al.*[30] showed that conyzic acid, *seco*-nidoresedic acid and strictic acid were identical. Further, there was a confusion in the literature regarding the orientation of methyl groups at C-8 and C-9 positions in strictic acid. This situtation was finally clarified[25] by performing photochemical transformations.

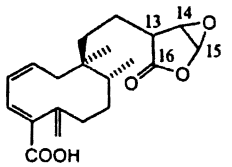
So far from the genus *Pulicaria*, flavones[31], acetylenes[32], caryophyllene derivatives[33], lactones[34], thymol derivatives[33,35] and clerodane[36] have been isolated. Chemical investigation of the whole plants of *P. angustifolia* afforded three new diterpenes, viz. 15-desmethoxy-16-oxo-15,16*H*-*seco*-nidoresedic(strictic)acid (**28**), 15-oxo-14,16*H*-*seco*-nidoresedic(strictic)acid (**29**), 16-oxo-14,15-epoxy-*seco*-nidoresedic(strictic)acid (**30**) in addition to methyl-5-α-hydroxyconyscabroate (**31**).



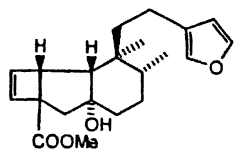
28



29



30



31

The molecular formula of the methyl ester of **28** was $C_{21}H_{28}O_4$ and its ir spectrum indicated the presence of an ester and a lactone functions (1765 and 1720 cm^{-1}). The ^1H nmr spectrum was in part similar to that of the methyl ester of strictic acid[27]. However, the signals of the β-substituted furan were replaced by a doublet triplet at δ 4.73 (2H) and a triplet of triplet at δ 7.09 (1H), which are typical for the lactone moiety in **28**.

The ^1H nmr spectral data of **29**, which had the same molecular formula as **28**, was also similar to that of methyl strictiate[27]. This time the furan signals were replaced by a

doublet at δ 4.76 (2H) and triplet of triplet at δ 5.84 exhibiting that the isomeric 15-acid lactone was present.

The molecular formula $C_{21}H_{28}O_5$ of methyl ester of **30** indicated that this compound differed from **28** and **29** by an additional oxygen. The ^1H nmr of **30** indicated that this oxygen should be placed at C-14 and C-15. A doublet of doublet at δ 3.87 was coupled with a doublet broad at δ 5.60 and with a multiplet at δ 2.77. The chemical shifts and the couplings required a 14,15-epoxide. The remaining signals, except those for H-12, were again very similar to those of **28** and **29**.

Experimental

Nmr spectra were recorded on a Bruker WM 400 instrument and chemical shifts being reported relative to δ_{TMS} = 0.00 ppm, mass spectra on a Varian MAT 711 at 70 eV direct inlet, and ir spectra ($CDCl_3$) on a Backman IR 9 spectrophotometer in CCl_4. Optical rotation was measured on a Perkin-Elmer polarimeter.

The air-dried aerial parts (2 kg) and roots (1.5 kg) of *Solidago altissima* collected from Jaipur and voucher deposited in RUBL-Herbarium, Jaipur, were extracted with Et_2O-petrol (1 : 2) for 24 h and the concentrated extract was column chromatographed over silica gel. CC fractions of the aerial parts (A) and the roots (R) were as follows : 1 (petrol), 2 (Et_2O-petrol, 1 : 4), 3 (Et_2O-petrol, 1 : 1) and 4 (Et_2O). Prep tlc of 3A (CH_2Cl_2-C_6H_6-Et_2O, 4 : 4 : 1) gave solidago lactone-VII **10** (50 mg; R_f 0.5), the corresponding tiglate **11** (60 mg; R_f 0.4) and solidago lactone-V **9** (20 mg; R_f 0.7). Tlc of 4A (same solvents system) afforded each solidago lactones II and III (25 mg; **7**, **8**, R_f 0.7, 0.4). Fraction 2R gave kolavenic acid (**4**; 150 mg). Tlc of 3R after addition of CH_2N_2 (Et_2O-petrol, 2 : 3) afforded methyl-6β-angeloyloxy- and 6β-tigloyloxy-*cis*-kolavenoates (15 mg **12**, 20 mg **13**; R_f 0.7, 0.6), methyl 7α-acetoxykolavenoate (20 mg **6**; R_f 0.5) and methyl 2-oxo-kolavenoate (15 mg **5**; R_f 0.4) and hydroperoxyclerodane (15 mg **2**; R_f 0.3). Repeated tlc of 4R (CH_2Cl_2-C_6H_6-Et_2O 4 : 4 : 1, several developments) gave solidagonal acid (5 mg **1**; R_f 0.7), solidagolactone-VII and the corresponding tiglate (10 mg **10**, **11**; R_f 0.6, 0.5), solidagolactones-II and III (10 mg **7**,**8**), solidagolactone-V (6 mg **9**) and 2-oxo-kolavenic acid lactone (20 mg **3**; R_f 0.15).

The air-dried aerial parts (2 kg) of *G. maderaspatana* Poir. (supplied by M/S United Chemicals and Allied Products, Calcutta, voucher deposited at RUBL Herbarium, Jaipur) were extracted with Et_2O-petrol-MeOH (1 : 1 : 1) at room temperature for 24 h. Concentrated extract was chromatographed over silica gel and following fractions were obtained : 1 (petrol), 2 (petrol-Et_2O, 3 : 1), 3 (petrol-Et_2O, 1 : 1) and 4 (Et_2O). Fraction 2 showed the presence of a complex mixture of diterpene acids. Therefore, it was subjected to methylation with ethereal solution of CH_2N_2. All diterpene acids were obtained as their methyl esters. Its separation on tlc was again difficult. It was finally separated by hplc, (MeOH-H_2O, 9 : 1) RP 18 (analytical) furnishing 10-*epi*-nidoresedic ci (15 mg **18**; R_t 11.8 min), strictic acid (50 mg **27**; R_t 12.7 min), centipedic acid (85 mg **26**; R_t 15.0 min) and hardwickiic acid (50 mg **16**; R_t 16.6 min). Addition of CH_2N_2 in fraction 3 and subsequent separation by hplc (MeOH-H_2O, 9 : 1) afforded 15-methoxy-16-oxo-15,16*H*-strictic acid (10 mg **24**; R_t 6.6 min), **21** (15 mg), **22** (8 mg; R_t 7.2 min), *nor*-strictic acid (12 mg **25**; R_t 7.9 min), *nor*-hardwickiic acid (5 mg **23**; R_t 9.4 min) and 2-α-acetoxyhardwickiic acid (21 mg **17**; R_t 12.4 min). Fraction 4 gave **24** (10 mg) after tlc.

Air-dried whole plant (1 kg) of *P. angustifolia* DC. (collected from Ramgarh, Rajasthan and voucher deposited in RUBL Herbaruim, Jaipur) was extracted with Et_2O-petrol (1 : 2) at room temperature for 12 h. Concentrated extract was column chromatographed and fractions collected as 1 (petrol), 2 (Et_2O-petrol, 1 : 4), 3 (Et_2O-petrol, 1 : 1) and 4 (Et_2O). Ethereal solution of diazomethane was added to fractions 2, 3 and 4. Prep.tlc of fraction 2 (Et_2O-petrol, 1 : 10) gave **31** (6 mg; R_f 0.5). Tlc of fraction 3 (C_6H_6-CH_2Cl_2-Et_2O, 4.5 : 4.5 : 1) gave **30** (5 mg; R_f 0.45). Tlc of fraction 4 (C_6H_6-CH_2Cl_2-Et_2O; 1 : 1 : 1) afforded **28** (5 mg; R_f 0.5) and **29** (6 mg; R_f 0.4). The identity of known compounds was established by direct comparison or by comparing their spectral data from literature. The structures of new natural products were deduced from high field ^1H nmr, high resolution mass and noe difference spectroscopy which allowed the assignment of the stereochemistry.

Solidagonal acid methyl ester (**1**) : Colourless oil; ν_{max} (CCl_4) 1720 (CHO, CO_2R), 1665, 1645 cm^{-1} (C=C); ^1H nmr δ($CDCl_3$) 2.33 (1H, dd br, *J* 15, 7 Hz, H-1), 2.17 (1H, ddq, *J* 15, 10, 1 Hz, H-1′), 9.96 (1H, s, H-3), 1.65 (1H, ddd, *J* 12.5, 3, 3 Hz, H-6), 1.35 (1H, m, H-6′), 1.55 (2H, m, H-7), 1.45 (1H, ddq, *J* 10, 4, 7 Hz, H-8), 1.56 (1H, dd, *J* 10, 7 Hz, H-10), 1.40 (2H, m, H-11), 2.05 (1H, ddd, *J* 13, 13, 12 Hz, H-12), 1.96 (1H, ddd, *J* 13, 6, 12 Hz, H-12′), 5.66 (1H, tq, *J* 1, 1 Hz, H-14), 2.15 (3H, d, *J* 1 Hz, H-16), 0.81 (3H, d, *J* 7 Hz, H-17), 2.02 (3H, dd, *J* 2, 1 Hz, H-18), 0.92 (3H, s, H-19), 0.85 (3H, s, H-20), 3.68 (3H, s, COOMe); *m/z* (rel.int.) 332.235 [M^+] (24) (calc. for $C_{21}H_{32}O_3$: 332.235), 317 [M-Me]$^+$ (9), 301 [M-OMe]$^+$ (10), 300 [M-MeOH]$^+$ (12), 285 [300-Me]$^+$ (20), 205 [M-CH_2-CH_2-C(Me)=$CHCO_2Me$]$^+$ (40), 95 (100); [α]$_D$ −111° ($CHCl_3$; *c* 0.15).

Methyl-3β-hydroperoxy-4,18-dehydro-3,4-dihydrokolavenoate (**2**) : Colourless oil; ν_{max} (CCl_4) 3520 (OOH),

1715 (C=CCO_2R), 1645 cm^{-1} (C=C); ^1H nmr δ ($CDCl_3$) 4.60 (1H, dd br, *J* 4, 2 Hz, H-3), 1.55 (1H, m, H-10), 1.40 (2H, m, H-11), 1.97 (1H, ddd, *J* 13,13, 5.5 Hz, H-12), 1.83 (1H, ddd, *J* 13, 12, 6 Hz, H-12′), 5.63 (1H, tq, *J* 1, 1 Hz, H-14), 2.15 (3H, d, *J* 1 Hz, H-16), 0.80 (3H, d, *J* 7 Hz, H-17), 4.85 (1H, s br, H-18), 4.75 (1H, s br, H-18′), 1.05 (3H, s, H-19), 0.72 (3H, s, H-20), 3.67 (3H, s, COOMe); *m/z* (rel.int.) 332.235 $[M-H_2O]^+$ (5) (calc. for $C_{21}H_{32}O_3$: 332.235), 317 $[M-OOH]^+$ (28), 301 [332-OMe]$^+$ (9), 300 [M-MeOH]$^+$ (6), 285 [300-Me]$^+$ (12), 189 $[C_{14}H_{21}]^+$ (42), 95 (84), 55 (100).

Reduction of **2** *to the alcohol* **14** : A solution of **2** (10 mg) in MeOH was treated with triphenyl phosphine (10 mg) for 1 h at room temperature. The solvent wass removed under reduced pressure and the residue purified by prep. tlc (CH_2Cl_2-C_6H_6-Et_2O; 4 : 4 : 1) to give **14** (7 mg) as a colourless oil. ^1H nmr spectrum of the alcohol was similar to that of **2** except that the signal at δ 8.00 was missing with slight upfield shift of H-3 proton; *m/z* (rel.int.) 334 $[M]^+$(6), 316 $[M-H_2O]^+$ (20).

16-Hydroxy-2-oxo-kolavenic-15-oic acid lactone (**3**) : Colourless gum; ν_{max} (CCl_4) 1785, 1750 (γ-lactone), 1670 (C=C–C=O) cm^{-1}; ^1H nmr δ ($CDCl_3$) 5.84 (1H, tt, *J* 1.5, 1.5 Hz, H-14), 5.74 (1H, s br, H-3), 4.72 (2H, d, *J* 1.5 Hz, H-16), 2.41 (1H, dd, *J* 18, 14 Hz, H-1α), 2.26 (1H, dd, *J* 18, 3 Hz, H-1β), 2.28 (2H, m, H-12), 1.90 (3H, d, *J* 1.5 Hz, H-18), 1.86 (1H, dd, *J* 14, 3 Hz, H-10), 1.15 (3H, s, H-19), 0.88 (3H, d, *J* 7 Hz, H-17), 0.85 (3H, s, H-20); *m/z* (rel.int.) 316.204 $[M]^+$ (12) (calc. for $C_{20}H_{28}O_3$: 316.204), 301 [M-Me]$^+$ (8), 288 [M-CO]$^+$ (6), 219 $[M-C_5H_5O_2]^+$ (18), 205 $[M-C_6H_7O_2]^+$ (5), 57 (100).

2α-Acetoxyhardwickiic acid (**17**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1760, 1730 (OAc), 1715 cm^{-1} (C=CCO_2R); ^1H nmr δ ($CDCl_3$) 5.42 (1H, ddd, *J* 7, 2, 2.5 Hz, H-2β), 6.42 (1H, d br, *J* 2.5 Hz, H-3), 6.30 (1H, s br, H-14), 7.34 (1H, dd, *J* 1.5, 1.5 Hz, H-15), 7.23 (1H, s br, H-16), 0.86 (3H, d, *J* 7 Hz, H-17), 1.35 (3H, s, H-19), 0.78 (3H, s, H-20), 3.70 (3H, s, COOMe), 2.08 (3H, s, OAc); *m/z* (rel.int.) 388.224 $[M]^+$ (12) (calc. for $C_{23}H_{32}O_5$: 388.224), 346 [M-ketene]$^+$ (12), 345 [M-Ac]$^+$ (22), 328 [M-AcOH]$^+$ (4), 314 [345-OMe]$^+$ (8), 313 [345-MeOH]$^+$ (9), 299 [314-Me]$^+$ (6), 95 (34), 81 (38), 61 (100); $[\alpha]_D$ –1.1° ($CHCl_3$; *c* 2.07).

10-epi-*Nidoresedic acid* (**18**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1700 cm^{-1} (C=C–C=C–CO_2R); ^1H nmr δ ($CDCl_3$) 6.01 (1H, dd br, *J* 10, 5.5 Hz, H-1), 6.18 (1H, dd br, *J* 10, 5.5 Hz, H-2), 6.64 (1H, d br, *J* 5.5 Hz, H-3), 2.15 (1H, d br, *J* 5.5 Hz, H-10), 6.20 (1H, s br, H-14), 7.31 (1H, dd, *J* 1.5, 1.5 Hz, H-15), 7.13 (1H, s br, H-16), 1.02 (3H, d, *J* 7 Hz, H-17), 1.17 (3H, s, H-19), 0.92 (3H, s, H-20), 1.40 (1H, ddd, *J* 13.5, 13.5, 3.5 Hz, H-6α), 2.48 (1H, ddd, *J* 13.5, 3.5, 3.5 Hz, H-6β), 1.24 (1H, dddd, *J* 13.5, 3.5, 3.5, 3.5, Hz, H-7α), 1.62 (1H, m, H-7β), 1.84 (1H, ddq, *J* 3.5, 3.5, 7 Hz, H-8), 2.14 (1H, ddd, *J* 13, 13, 5 Hz, H-11), 1.60 (1H, m, H-11′), 2.24 (1H, ddd, *J* 13, 13, 5 Hz, H-12), 2.07 (1H, ddd, *J* 13, 13, 5 Hz, H-12′), 3.72 (3H, s, COOMe); *m/z* (rel.int.) 328.203 $[M]^+$ (8) (calc. for $C_{21}H_{28}O_3$: 328.203), 313 [M-Me]$^+$ (8), 297 [M-OMe]$^+$ (4), 285 [313-CO]$^+$ (10), 151 (98), 81 (100); $[\alpha]_D$ –66.1° ($CHCl_3$; *c* 1.0).

*16-Oxo-15,16*H-*hardwickiic acid* (**20**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1770 (γ-lactone), 1715 cm^{-1} (C=C–CO_2R); ^1H nmr δ ($CDCl_3$) 6.60 (1H, dd br, *J* 4, 3 Hz, H-3), 7.09 (1H, tt, *J* 1.5, 1.5 Hz, H-14), 4.76 (2H, dt, *J* 1.5, 1.5 Hz, H-15), 0.83 (3H, d, *J* 7 Hz, H-17), 1.26 (3H, s, H-19), 0.78 (3H, s, H-20), 3.68 (3H, s, COOMe); *m/z* (rel.int.) 314.188 [M-MeOH]$^+$ (100) (calc. for $C_{20}H_{26}O_3$: 314.188), 315 [M-OMe]$^+$ (20), 299 [314-Me]$^+$ (2), 271 [299-CO]$^+$ (10), 139 (30), 107 (26) and 61 (50); $[\alpha]_D$ –62° ($CHCl_3$; *c* 1.38).

*15-Methoxy-16-oxo-15,16*H-*hardwickiic acid* (**21**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1780 (γ-lactone), 1710 cm^{-1} (C=C–CO_2R); ^1H nmr δ ($CDCl_3$) 6.60 (1H, dd br, *J* 4, 3 Hz, H-3), 6.76 (1H, dt, *J* 1.5, 1.5 Hz, H-14), 5.75 (1H, dt, *J* 1.5, 1.5 Hz, H-15), 0.81 (3H, d, *J* 7 Hz, H-17), 1.27 (3H, s, H-19), 0.77 (3H, s, H-20), 3.68 (3H, s, COOMe), 3.58 (3H, s, OMe); *m/z* (rel.int.) 344.198 [M-MeOH]$^+$ (20) (calc. for $C_{21}H_{28}O_4$: 344.198), 329 [344-Me]$^+$ (90), 297 [329-MeOH]$^+$ (1), 61 (100); $[\alpha]_D$ –30.8° ($CHCl_3$; *c* 0.37).

15-Methoxy-16-oxo-nidoresedic acid (**22**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1775 (γ-lactone), 1710 cm^{-1} (C=C–CO_2R); ^1H nmr δ ($CDCl_3$) 6.15 (2H, m, H-1 and H-2), 6.73 (1H, m, H-3), 2.29 (1H, sbr, H-10), 6.75 (1H, dt, *J* 1.5, 1.5 Hz, H-14), 5.74 (1H, dt, *J* 1.5, 1.5 Hz, H-15), 0.87 (3H, d, *J* 7 Hz, H-17), 1.08 (3H, s, H-19), 0.91 (3H, s, H-20), 3.72 (3H, s, COOMe), 3.57 (3H, s, OMe); *m/z* (rel.int.) 374.209 $[M]^+$ (2) (calc. for $C_{22}H_{30}O_5$: 374.209), 342 [M-MeOH]$^+$ (30), 327 [342-Me]$^+$ (90), 295 [327-MeOH]$^+$ (20), 128 (100); $[\alpha]_D$ –120.8° ($CHCl_3$; *c* 0.23).

nor-*Hardwickiic acid* (**23**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1730 (CO_2R), 1710 cm^{-1} (C=CCO_2R); ^1H nmr δ ($CDCl_3$) 6.58 (1H, dd, *J* 4, 3 Hz, H-3), 0.84 (3H, d, *J* 7 Hz, H-17), 1.27 (3H, s, H-19) 0.79 (3H, s, H-20), 3.68 (3H, s, COOMe), 3.66 (3H, s, OMe); *m/z* (rel.int.) 322.214 $[M]^+$ (5) (calc. for $C_{19}H_{30}O_4$: 322.214), 291 [M-OMe]$^+$ (20), 290 [M-MeOH]$^+$ (100), 275 [290-Me]$^+$ (5), 260 [275-Me]$^+$ (4), 235 [M-CH_2-CH_2-CO_2Me]$^+$ (12), 203 [235-MeOH]$^+$ (20), 175 [203-CO]$^+$ (20), 69 (100); $[\alpha]_D$ –36° ($CHCl_3$; *c* 0.10).

*15-Methoxy-16-oxo-15,16*H-*strictic acid* (**24**) : It was

isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1780 (γ-lactone), 1720 (C=C–C=C–CO_2R), 1250 cm^{-1}; ^{1}H nmr δ ($CDCl_3$) 5.40 (1H, dddd, *J* 11, 4, 13, 2 Hz, H-1), 5.93 (1H, ddd, *J* 11, 2.5, 1.5 Hz, H-2), 7.25 (1H, dd br, *J* 4, 2.5 Hz, H-3), 2.26 (1H, dd, *J* 13, 13 Hz, H-10α), 1.78 (1H, ddd, *J* 13, 2, 1.5 Hz, H-10β), 6.77 (1H, s br, H-14), 5.74 (1H, s br, H-15), 0.78 (3H, d, *J* 7 Hz, H-17), 5.06 (1H, s br, H-19), 4.84 (1H, s br, H-19′), 0.73 (3H, s, H-20), 3.77 (3H, s, COOMe), 3.69 (3H, s, OMe); *m/z* (rel.int.) 374.209 $[M]^+$ (8) (calc. for $C_{22}H_{30}O_5$: 374.209), 343 $[M-OMe]^+$ (10), 342 $[M-MeOH]^+$ (12), 327 $[342-Me]^+$ (6), 310 $[342-MeOH]^+$ (8), 61 (100); $[\alpha]_D$ –135° ($CHCl_3$; *c* 0.24).

nor-*Strictic acid* (**25**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1730 (CO_2R), 1710 cm^{-1} (C=C–C=C–CO_2R); ^{1}H nmr δ ($CDCl_3$) 5.35 (1H, dddd, *J* 11, 4, 13, 2 Hz, H-1), 5.93 (1H, ddd, *J* 13, 2.5, 2.5 Hz, H-2), 7.25 (1H, dd, br, *J* 4, 2.5 Hz, H-3), 2.22 (1H, dd, *J* 13, 13 Hz, H-10α), 0.81 (3H, d, *J* 7 Hz, H-17), 5.06 (1H, s br, H-19), 4.84 (1H, s br, H-19′), 0.69 (3H, s, H-20), 3.77 (3H, s, COOMe), 3.69 (3H, s, OMe); *m/z* (rel.int.) 320.198 $[M]^+$ (8) (calc. for $C_{19}H_{28}O_4$: 320.198), 289 $[M-OMe]^+$ (12), 288 $[M-MeOH]^+$ (18), 273 $[288-Me]^+$ (8), 256 $[288-MeOH]^+$ (10), 201 $[288-CH_2-CH_2-CO_2Me]^+$ (24), 173 $[201-CO]^+$ (30), 55 (100); $[\alpha]_D$ –26° ($CHCl_3$; *c* 0.41).

*15-Desmethoxy-16-oxo-15,16*H*-strictic acid* (**28**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1765 (γ-lactone), 1720 cm^{-1} (C=C–CO_2R); ^{1}H nmr δ ($CDCl_3$) 5.40 (1H, dddd, *J* 11, 4, 13, 2 Hz, H-1), 5.93 (1H, ddd. *J* 11, 2.5, 1.5 Hz, H-2), 7.26 (1H, dd br, *J* 4, 2.5 Hz, H-3), 2.61 (1H, ddddd, *J* 13.5, 2, 2, 2, 2 Hz, H-6α), 2.06 (1H, ddd, *J* 13.5, 2, 2 Hz, H-6β), 1.55 (1H, m, H-7α), 0.81 (1H, m, H-7β), 1.36 (1H, ddq, *J* 10, 3, 7 Hz, H-8), 2.25 (1H, dd, *J* 13, 13 Hz, H-10α), 1.78 (1H, dddd, *J* 13, 2, 1.5, 1.5 Hz, H-10β), 1.50 (2H, m, H-11), 2.25 (2H, m, H-12), 7.09 (1H, tt, *J* 1.5, 1.5 Hz, H-14), 4.73 (2H, dt. *J* 1.5, 1.5 Hz, H-15), 0.72 (3H, d, *J* 7 Hz, H-17), 5.02 (1H, dd, *J* 2, 1 Hz, H-19), 4.79 (1H, s br, H-19′), 0.67 (3H, s, H-20), 3.77 (3H, s, COOMe); *m/z* (rel.int.) 344.199 $[M]^+$ (6) (calc. for $C_{21}H_{28}O_4$: 344.199), 314 $[M-CH_2O]^+$ (26), 312 $[M-MeOH]^+$ (32), 297 $[312-Me]^+$ (10), 91 (80), 55 (100).

*15-Oxo-14,16*H*-strictic acid* (**29**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1790 (γ-lactone), 1725 cm^{-1} (C=C–CO_2R); ^{1}H nmr δ ($CDCl_3$) 5.25 (1H, dddd, *J* 11, 4, 13, 2 Hz, H-1), 5.94 (1H, ddd, *J* 11, 2.5, 1.5 Hz, H-2), 7.26 (1H, dd br, *J* 4, 2.5 Hz, H-3), 2.60 (1H, dddd, *J* 13.5, 2, 2, 2 Hz, H-6α), 2.06 (1H, ddd, *J* 13.5, 2, 2 Hz, H-6β), 1.55 (1H, m, H-7α), 0.81 (1H, m, H-7β), 1.35 (1H, ddq, *J* 10, 3, 7 Hz, H-8), 2.27 (1H, dd, *J* 13, 3 Hz, H-10α), 1.70 (1H, dddd, *J* 13, 2, 1.5, 1.5 Hz, H-10β), 1.50 (2H, m, H-11), 2.25 (2H, m, H-12), 5.84 (1H, tt, *J* 1.5, 1.5 Hz, H-14), 4.76 (2H, d, *J* 1.5, Hz, H-16), 0.75 (3H, d, *J* 7 Hz, H-17), 5.07 (1H, dd, *J* 2, 1 Hz, H-19), 4.84 (1H, s br, H-19′), 0.68 (3H, s, H-20), 3.77 (3H, s, COOMe); *m/z* (rel.int.) 344.199 $[M]^+$ (6) (calc. for $C_{21}H_{28}O_4$: 344.199), 313 $[M-OMe]^+$ (6), 312 $[M-MeOH]^+$ (9), 91 (65), 55 (100).

16-Oxo-14,15-epoxystrictic acid (**30**) : It was isolated as its methyl ester, colourless gum; ν_{max} (CCl_4) 1810 (γ-lactone), 1720 cm^{-1} (C=C–CO_2R); ^{1}H nmr δ ($CDCl_3$) 5.36 (1H, dddd, *J* 11, 4, 13, 2 Hz, H-1), 5.93 (1H, ddd, *J* 11, 2.5, 1.5 Hz, H-2), 7.26 (1H, dd, *J* 4, 2.5 Hz, H-3), 2.65 (1H, ddddd, *J* 13.5, 2, 2, 2, 2 Hz, H-6α), 2.09 (1H, ddd, *J* 13.5, 2, 2 Hz, H-6β), 1.57 (1H, m, H-7α), 0.85 (1H, m, H-7β), 1.37 (1H, ddq, *J* 10, 3, 7 Hz, H-8), 2.23 (1H, dd, *J* 13, 3 Hz, H-10α), 1.72 (1H, dddd, *J* 13, 2, 1.5, 1.5 Hz, H-10β), 1.50 (2H, m, H-11), 1.82 (1H, m, H-12), 1.72 (1H, m, H-12′), 2.77 (1H, m, H-13), 3.87 (1H, dd, *J* 2.5, 2 Hz, H-14), 5.60 (1H, d br, *J* 2.5 Hz, H-15), 0.79 (3H, d, *J* 7 Hz, H-17), 5.06 (1H, dd, *J* 2, 1 Hz, H-19), 4.84 (1H, s br, H-19′), 0.70 (3H, s, H-20), 3.78 (3H, s, COOMe); *m/z* (rel.int.) 360.194 $[M]^+$ (3) (calc. for $C_{21}H_{28}O_5$: 360.194), 345 $[M-Me]^+$ (1), 329 $[M-CH_3O]^+$ (5), 328 $[M-MeOH]^+$ (2), 299 $[328-CHO]^+$ (6), 91 (72), 55 (100).

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