

Semisynthetic Derivatives of Quassin

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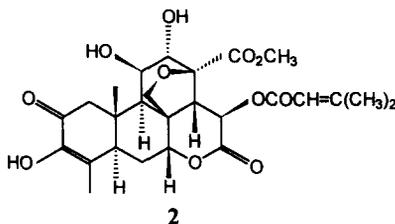
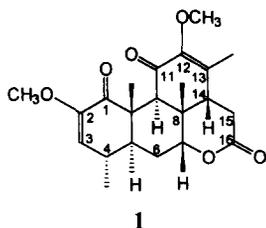
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Abstract: The natural product quassin has been modified in order to produce compounds with potential antimalarial action. The modifications include demethylation, reduction of the keto function, esterification with simple organic acids and - to enhance the uptake through the biological barriers and increase the stability of the compounds - with lipoamino acids. © 1998 Published by Elsevier Science Ltd. All rights reserved.

INTRODUCTION

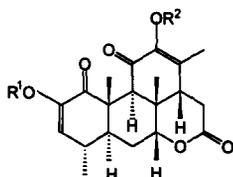
The bitter degraded triterpenoid quassinoids have been identified as the active constituents of plants from the Simaroubaceae which are used pantropically to treat malaria, leukaemia, amoebiasis and other ailments.^{1,2} The work described in this paper is a continuation of our studies on the chemical modification of quassinoids as potential antimalarial agents.^{3,4}



It has been demonstrated that quassinoids are potent inhibitors of protein synthesis and although the active site is not fully known it has been established that the state of oxidation and substitution in ring A, the presence of a C-8 methylene-oxygen bridge to C-11 or to C-13 and the nature of the C-15 substituent have marked effects on antiplasmodial activity.⁵ It has been suggested that an ester side chain may increase lipophilicity of the compound, thus aiding delivery to the site of action and that the branched or unsaturated nature of the ester moiety may be important for effective interaction or bonding at the site of action.⁶ The parent quassinoid, quassin 1 which is inactive against tumour cells and against plasmodia differs chemically from potent quassinoids such as brusatol 2. There are three major chemical differences between quassin and brusatol, which contains (i) an extra substituent at C-15, (ii) different substituents in ring A and (iii) a methylene-oxygen bridge in ring C. In order to investigate the effect on biological activity of introducing various substituents on the quassin molecule a series of quassin derivatives has been prepared.

DISCUSSION

To study the structure activity relationship of quassin analogues, different compounds were synthesised systematically varying the substituents at the C-2, C-12 and C-15 positions.



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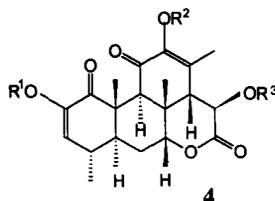
3	R ¹	R ²
a	H	CH ₃
b	COCH ₃	CH ₃
c	COC ₆ H ₅	CH ₃
d	COCH=C(CH ₃) ₂	CH ₃
e	COCH ₂ C(CH ₃) ₃	CH ₃
f	CO(CH ₂) ₄ CH ₃	CH ₃
g	CO(CH ₂) ₁₆ CH ₃	CH ₃
h	CH ₂ O(CH ₂) ₂ OCH ₃	CH ₃
i	COCH ₂ [NHOCOC(CH ₃) ₃]	CH ₃
j	COCH[NHOCOC(CH ₃) ₃]CH(CH ₃) ₂	CH ₃
k	COCH[NHOCOC(CH ₃) ₃]CH(CH ₃)C ₂ H ₅	CH ₃
l	COCH[NHOCOC(CH ₃) ₃]CH ₂ C ₆ H ₅	CH ₃
m	COCH[NHOCOC(CH ₃) ₃](CH ₂) ₇ CH ₃	CH ₃
n	COCH[NHOCOC(CH ₃) ₃](CH ₂) ₉ CH ₃	CH ₃
o	COCH[NHOCOC(CH ₃) ₃](CH ₂) ₁₁ CH ₃	CH ₃
p	COCH[NHOCOC(CH ₃) ₃](CH ₂) ₁₇ CH ₃	CH ₃
r	H	H
s	COCH ₃	H
t	COC ₆ H ₅	H

Modifications at C-2

For the preparation of C-2 modified quassin analogues, quassin was demethylated with 10% HCl in acetic acid to yield norquassin (**3a**). Norquassin (**3a**) was acylated with the corresponding acid, anhydride or acid chloride to yield the series of esters **3b-3g**. The presence of methoxyethoxymethylether group in quassinoids was reported to enhance *in vitro* antimalarial activity.⁷ To examine the effect of the presence of methoxyethoxymethylether at C-2, compound **3h** was prepared by treatment of compound **3a** with methoxyethoxymethyl chloride. Amino acid esters **3i-3l** were prepared from N-(tert.butoxycarbonyl)-glycine, -L-valine, -L-isoleucine and -L-phenylalanine respectively.

The lipoamino acids and their oligomers provide an excellent means of enhancing the lipophilicity of different conjugating compounds and also increase the biological stability of the drugs by protecting them from

enzymatic degradation.^{8,9} Lipophilic quassin analogues were prepared from lipoamino acids of increasing lipophilicity. Reaction of compound **3a** with 2-tert.butoxycarbonylamino-decanoic, -dodecanoic, tetradecanoic and -eicosanoic acid, using standard solution phase peptide synthetic methods, afforded esters **3m-3p**. Since the starting lipoamino acids were racemic, the compounds containing lipoamino acyl substituents were diastereomeric mixtures.



4	R ¹	R ²	R ³
a	CH ₃	CH ₃	H
b	CH ₃	CH ₃	COCH=C(CH ₃) ₂
c	CH ₃	CH ₃	COCH ₃
d	CH ₃	CH ₃	COCH[NHOCOC(CH ₃) ₃](CH ₂) ₇ CH ₃
e	CH ₃	CH ₃	CH ₂ OCH ₂ CH ₂ OCH ₃
f	H	CH ₃	H
g	COCH[NHOCOC(CH ₃) ₃](CH ₂) ₇ CH ₃	CH ₃	H
h	COCH=C(CH ₃) ₂	CH ₃	COCH=C(CH ₃) ₂
i	H	H	COCH=C(CH ₃) ₂
j	H	H	H
k	COCH[NHOCOC(CH ₃) ₃](CH ₂) ₇ CH ₃	H	H
l	COCH ₃	COCH ₃	COCH ₃
m	CO(CH ₂) ₄ CH ₃	CO(CH ₂) ₄ CH ₃	CO(CH ₂) ₄ CH ₃
n	CO(CH ₂) ₁₆ CH ₃	CO(CH ₂) ₁₆ CH ₃	CO(CH ₂) ₁₆ CH ₃

Modification at C-15

The synthesis of C-15 modified quassin analogues commenced with hydroxyquassin **4a**, possessing a β -hydroxyl group at C-15, which was prepared and reported previously.^{3,10} Acylation of hydroxyquassin **4a** with 3,3-dimethylacryloyl chloride resulted in compound **4b** with the same C-15 substituent as brusatol. The C-15 acetylated product **4c** was also prepared by reacting compound **4a** with acetic anhydride.

To enhance the lipophilicity, quassin conjugate **4d** was prepared by reacting compound **4a** with 2-(tert-butoxycarbonylamino)-decanoic acid.

Acylation of the OH at C-15 resulted approximately in a 0.5 ppm chemical shift movement downfield of the C-15 H signal in the ¹H-NMR of the compounds, clearly indicating the completion of acylation reactions.

To examine the effect of the presence of methoxyethoxymethylether at C-15, compound **4e** was prepared by treatment of compound **4a** with methoxyethoxymethyl chloride.

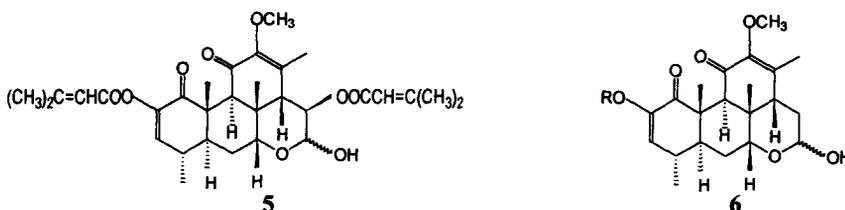
Modification at C-2 and C-12

Compound **3** was reacted with BBr₃ resulting in production of diol **3r**. Demethylation at C-12 of acetate **3b** and benzoate **3c** with BBr₃ provided C-12 hydroxy esters **3s** and **3t** respectively. The presence of a free hydroxyl group at C-12 in quassinoids was reported to enhance biological activity.¹¹

Modification on the C-2 and C-15

Further analogues of quassin **1** were prepared from the C-15 substituted compounds. Hydrolysis of the C-2 methoxy group in hydroxyquassin **4a** was achieved with hydrochloric acid in acetic acid under reflux to provide norhydroxyquassin **4f**. Compound **4f** served as starting material for the preparation of C-2, and C-15 modified quassin analogues. When norhydroxyquassin **4f** was treated with one equivalent of 2-(*tert*-butoxycarbonylamino)-decanoic acid monoester **4g** containing the lipidic substituent on C-2 was obtained as the major product. This was confirmed by ¹H NMR examination, the protons of compound **4g** on C-3 and C-15 appeared as doublets at $\delta=6.13$ ppm and 4.5 ppm respectively.

Norhydroxyquassin **4f** provided diacrylate **4h** on esterification with an excess of 3,3-dimethylacryloyl chloride. In the ¹H NMR spectrum of compound **4h** the vinylic proton at C-3 had moved down field to $\delta=6.1$ ppm from 5.7 ppm of **4f**. A similar trend was observed in the case of the proton at C-15, a shift from $\delta=4.5$ ppm to 5.1 ppm was observed (see Experimental).



Modifications at C-2, C-12 and C-15

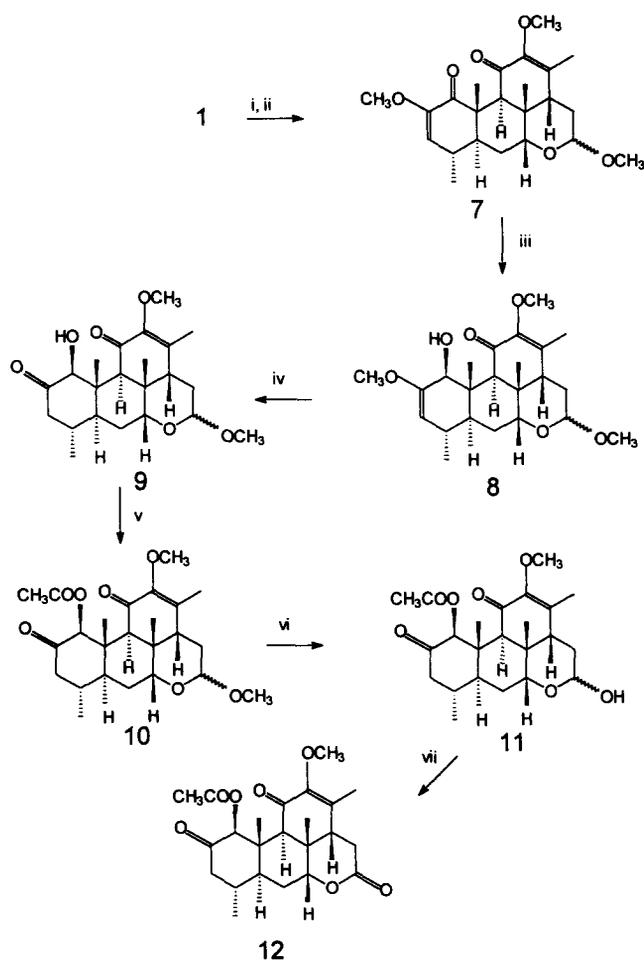
Exposure of ester **4b** to BBr₃ in dichloromethane at -78 °C hydrolysed the C-2 and C-12 methoxy groups to provide diol **4i**. Compound **4f** was reacted with BBr₃, resulting in formation of the 2,12,15-triol **4j**. Triol **4j** generated the C-2 monoester **4k**, by treatment with one equivalent of 2-(*tert* butoxycarbonylamino)-decanoic acid, indicating that position C-2 was the most reactive. The substituents at C-12 and C-15 remained unreactive. The positive reaction observed with ferric chloride (on thin layer chromatography plate) indicated the presence of a diosphenol group in the molecule and the ¹H NMR spectrum showed a doublet at $\delta=4.5$ ppm for H-15. However, when compound **4j** was reacted with excess of acetic anhydride, hexanoic anhydride and stearic acid, triacetate **4l**, trihexanoate **4m** and tristearate **4n** were formed respectively.

Further modifications at C-15

Diacrylate **4h** and esters **3j** and **3o** were reduced with sodium borohydride in ethanol at room temperature to yield diastereomeric hemiacetals **5**, **6a** and **6b** respectively.

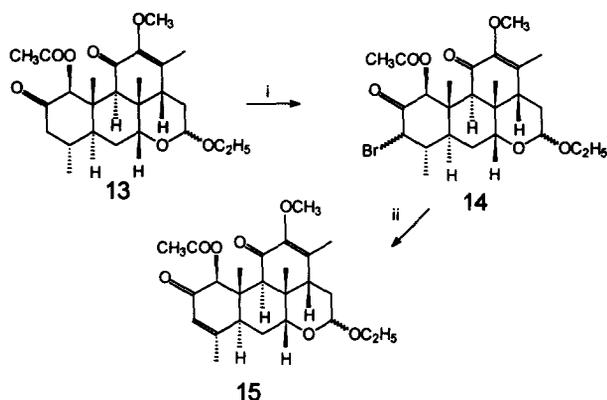
Synthesis of Glaucarubinone¹² analogues

Conversion of quassin **1** into the corresponding lactol with sodium borohydride followed by treatment with concentrated HCl in methanol at room temperature provided the methyl acetal **7** (scheme 1). Transformation of compound **7** and **9** was carried out according to the method of Nakamura *et al.*¹³ The carbonyl at C-1 was reduced with sodium borohydride in the presence of CeCl₃ in methanol at -10 °C to give enol ether **8**. Hydrolysis of the C-2 methoxy group in compound **8** proceeded smoothly with pyridinium *p*-toluene sulphonate in aqueous acetone to afford α -ketol **9**. Compound **9** was acetylated with acetic anhydride and dimethylaminopyridine (DMAP) in CH₂Cl₂ affording acetate **10**. The lactone in ring D was generated in two steps. Deprotection of acetal **10** with 10 % HCl



Scheme 1. Synthesis of glaucarubinone analogues. i) NaBH_4 , ii) HCl , iii) NaBH_4 , CeCl_3 , MeOH , iv) pyridinium *p*-toluene sulphonate in acetone, v) Ac_2O , DMAP, vi) 10 % HCl , THF, vii) PCC, CH_2Cl_2

in THF furnished lactol **11** which was transformed into lactone **12** with pyridinium chlorochromate (PCC) in CH_2Cl_2 . The double bond between C-3 and C-4 was introduced by the following procedure. The lactol in compound **11** was protected by treatment with concentrated HCl in ethanol resulting in compound **13**. Bromination of compound **13** with phenyltrimethylammonium tribromide (PTAT) in THF at 0°C gave rise to the C-3 brominated product **14**. Dehydrobromination of compound **14** with $\text{LiCO}_3\text{-LiBr}$ in dimethylformamide furnished the glaucarubinone analogue **15** (scheme 2). Compound **15** was fully characterised by ^1H NMR (see Experimental). The *in vitro* antimalarial activities of these compounds will be reported elsewhere.



Scheme 2. Synthesis of diene **15** i) PTAT, THF, ii) LiBr, LiCO₃, DMF

EXPERIMENTAL

UV Spectra were recorded on a Perkin-Elmer 402 Ultraviolet-Visible Spectrophotometer using spectroscopic grade methanol. ¹H NMR spectra (CDCl₃) were recorded on a Bruker WM 250 spectrometer, or Bruker AMX 400, or Bruker AM 500 spectrometer. Electron Impact (EI) mass spectra were recorded on a VG Analytical LTD ZAB IF Spectrophotometer. Fast atom bombardment (FAB) spectra were recorded on a VG analytical ZAB-SE spectrometer; samples were dissolved in a 2-nitrobenzyl alcohol plus sodium iodide matrix (MNOBA + NaI) unless otherwise stated. High resolution MS (M+H or M+Na). Thin layer chromatography analysis were performed on Merck aluminium backed precoated thin layer Kiesel gel 60 F₂₅₄ plates (0.25mm thick). Chromatograms were visualised by spraying with p-anisaldehyde solution (135 ml of ethanol, 5 ml of concentrated H₂SO₄, 1.5 ml acetic acid, 4 ml of p-anisaldehyde) and heating at 110°C. Column chromatography was carried out by flash technique using silica gel Sorbsil C 60-H (40-60µm) Rhone-Poulenc. The solvents were evaporated *in vacuo*.

Norquassin (3a): A mixture of quassin (**1**) (25 mg, 6.44 mmol), 10% HCl (15 ml), and glacial acetic acid (4 ml) was refluxed at 115°C for 2 h. The mixture was poured into water (15 ml), neutralised with 2 M NaOH, extracted with CHCl₃ (3x15 ml) and washed with brine. The organic layer was dried (MgSO₄), concentrated and the residue recrystallised from ethanol to yield 16 mg (69%) of norquassin (**3a**); grey-black with ferric chloride. MS (EI) m/z (%): 375 [M+H]⁺ (100), 360 (12), 331 (14), 313 (7), 181 (6). ¹H NMR: δ=5.75 (d, 1H, J=2.3 Hz, C-3 H), 5.6 (s, 1H, C-2 OH, exchangeable with D₂O), 4.3 (m, 1H, C-7 H), 3.7 (s, 3H, C-12 OCH₃), 3.0 (dd, J=6Hz and 18Hz 1H, C-15 H), 2.9 (s, 1H, C-9 H), 2.55 (m, 1H, C-4 H), 2.4 (dd, J=6Hz and 18Hz 1H, C-14 H), 2.2-1.5 (m, 3H, C-5 H, C-6 Hs, C-15 H), 1.85(s, 3H, C-13 CH₃), 1.6 (s, 3H, C-10 CH₃), 1.25 (s, 3H, C-8 CH₃), 1.1 (d, 3H, J=6.1 Hz, C-4 CH₃). Rf=0.77; CHCl₃:MeOH 95:5 (v/v).

2-O-desmethyl-2-O-acetylquassin (3b): To a cooled solution of norquassin (**3a**) (93 mg, 0.249 mmol) and DMAP

(45 mg, 0.367 mmol) in CH_2Cl_2 (5 ml) acetyl chloride (0.1 ml) was added and the reaction mixture stirred at room temperature for 15 hours. The mixture was diluted with CH_2Cl_2 (10 ml) washed with saturated aqueous NaHCO_3 (10 ml) and brine. The organic layer was dried (MgSO_4) and concentrated. The residue was purified by tlc (CHCl_3 :MeOH 95:5) to obtain 49 mg (41 %) of **3b** as a white solid. MS (FAB) m/z (%): 438 $[\text{M}+23]^+$ (100), 351 (30), 172 (14), 107 (14). ^1H NMR (B): δ =6.22 (d, 1H J =2.3 Hz, C-3H), 4.3 (m, 1H, C-7H), 3.63 (s, 3H, C-12 OCH_3), 3.1-2.95 (m, 1H, C-15), 3.0 (s, 1H, C-9 H), 2.6 (m, 1H, C-4), 2.5 (m, 1H, C-15 H), 2.35 (m, 1H, C-14 H), 2.2 (3H, s, CH_3CO), 2.2-1.95 (m, 3H, C-6 H, C-5 H), 1.85 (s, 3H, C-13 CH_3), 1.72 (s, 3H, C-10 CH_3) 1.23 (s, 3H, C-8 CH_3), 1.14 (d, 3H, J =6.1 Hz, C-4 CH_3).

2-O-desmethyl-2-O-benzoylquassin (3c): Compound **3c** (46 mg, 39%) was prepared from norquassin (**3a**) and benzoylchloride using the method described for **3b**. MS (FAB) m/z (%): 501 $[\text{M}+23]^+$ (100), 413 (19), 393 (7), 301 (2), 176 (16), 149 (16), 105 (44), 91 (12). High resolution MS: Calculated for $\text{C}_{28}\text{H}_{30}\text{O}_7\text{Na}$ (501.1889), Found=501.2029. ^1H NMR (B): δ =8.1-7.4 (m, 5H, aromatic-H's), 6.25 (d, 1H J =2.3 Hz, C-3H), 4.3 (m, 1H, C-7H), 3.65 (s, 3H, C-12 OCH_3), 3.1-2.95 (m, 1H, C-15), 3.0 (s, 1H, C-9 H), 2.6 (m, 1H, C-4), 2.5 (m, 1H, C-15 H), 2.4 (m, 1H, C-14 H), 2.2-1.95 (m, 3H, C-6 H, C-5 H), 1.85 (s, 3H, C-13 CH_3), 1.75 (s, 3H, C-10 CH_3) 1.25 (s, 3H, C-8 CH_3), 1.15 (d, 3H, J =6.1 Hz, C-4 CH_3). IR: ν_{max} 1710, 1680, 1630, 1590 cm^{-1} .

2-O-desmethyl-2-O-(3,3-dimethylacrylyl)quassin (3d): Compound **3d** (16.3 mg, 67%) was prepared from norquassin (**3a**) and 3,3-dimethylacryloyl-chloride using the method described for **3b**. Purification: CHCl_3 -MeOH 98:2 (v/v). MS (EI) m/z (%): 456 $[\text{M}]^+$ (30), 374 (62), 359 (14), 346 (13), 331 (14), 315 (11), 303 (9), 287 (15), 271 (14), 243 (16), 223 (21), 205 (26), 189 (29), 165 (45), 149 (97), 137 (47), 123 (53), 105 (77), 91 (100). ^1H NMR: δ =6.15 (d, 1H J =2.3 Hz, C-3 H), 5.8 (s, 1H, C-2'H), 4.25 (m, 1H, C-7 H), 3.6 (s, 3H, C-12 OCH_3), 3.1 (m, 1H, C-15 H), 3.0 (s, 1H, C-9 H), 2.6-2.3 (m, 2H, C-4 H, C-14 H), 2.18 (s, 3H, C-5' CH_3), 1.93 (s, 3H, C-4' CH_3), 1.87 (s, 3H, C-13 CH_3), 1.64 (s, 3H, C-10 CH_3), 1.23 (s, 3H, C-8 CH_3), 1.17 (d, 3H, J =6.1 Hz, C-4 CH_3).

2-O-desmethyl-2-O-tert-butylacetylquassin (3e): To a mixture of norquassin (**3a**) (30 mg, 0.0802 mmol), DMAP (14.3 mg, 0.117 mmol), EDC (22 mg, 0.115 mmol) in CH_2Cl_2 (5 ml) tert-butylacetic acid (0.1 ml) was added and the reaction mixture stirred for 1.5 hours at room temperature. The mixture was diluted with CH_2Cl_2 (15 ml), poured into saturated aqueous NaHCO_3 (10 ml), washed with brine, the organic phase dried (Na_2SO_4) and concentrated. The crude product was purified by tlc (CHCl_3 :MeOH 95:5 v/v, R_f =0.82) to obtain 16.5 mg, (44 %) of compound **3e**. MS (EI) m/z (%)=472 $[\text{M}]^+$ (12), 457 (6), 374 (43), 359 (12), 346 (13), 331 (19), 314 (8), 287 (6), 262 (6), 223 (7), 165 (9), 151 (15), 100 (42), 91 (41), 83 (24), 69 (78), 57 (100). High resolution MS: Calculated for $\text{C}_{27}\text{H}_{36}\text{O}_7\text{Na}$ (495.2359), Found=495.2886. ^1H NMR (B): δ =6.05 (d, 1H J =2.3 Hz, C-3 H), 4.25 (m, 1H, C-7 H), 3.65 (s, 3H, C-12 OCH_3), 3.05 (m, 1H, C-15 H), 2.95 (s, 1H, C-9 H), 2.6 (m, 2H, C-4 H, C-14 H), 2.45-2.4 (m, 3H, C-14 H, α - CH_2), 2.05-1.90 (m, 3H, C-6 H, C-5 H), 1.85 (s, 3H, C-13 CH_3), 1.6 (s, 3H, C-10 CH_3), 1.2 (s, 1H, C-8 CH_3), 1.1 (d, 3H, J =6.1 Hz, C-4 CH_3), 1.05 [s, 9 H, $\text{C}(\text{CH}_3)_3$].

2-O-desmethyl-2-O-hexylquassin (3f)

To a cooled (-5 °C) solution of norquassin (**3a**) (20 mg, 0.053 mmol) and DMAP (12 mg, 0.098 mmol) in CH_2Cl_2 (3 ml), hexanoic anhydride (0.25 ml) was added and reaction mixture stirred for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 (15 ml), washed with brine, dried (MgSO_4) and concentrated *in vacuo*. Chromatography of the crude product on a preparative TLC plate (SiO_2 , CHCl_3 :MeOH 95:5) yielded 8.6 mg (33%)

of hexanoate **3f**. MS (FAB) m/z (%) = 472 [M]⁺ (41), 458 (10), 388 (11), 374 (100) 359 (58), 346 (68), 331 (50), 315 (39), 287 (29), 262 (40), 245 (18), 223 (47), 203 (20), 179 (26), 152 (88), 137 (32), 99 (98). ¹H NMR (B): δ =6.1 (d, 1H, J =2.3 Hz, C-3 H), 4.3 (m, 1H, C-7 H), 3.67 (s, 3H, C-12 OCH₃), 3.05 (m, 1H, C-15 H), 2.96 (s, 1H, C-9 H), 2.60-2.40 (m, 4H, α -CH₂, C-4 H, C-14 H), 1.87 (s, 3H, C-13 CH₃), 1.67 (s, 3H, C-10 CH₃), 1.33 (m, 6H, 3 CH₂), 1.17 (s, 3H, C-8 CH₃), 1.14 (d, 3H, J =6.1 Hz, C-4 CH₃), 0.89 (m, 3H, CH₃). Rf=0.66 (CHCl₃:MeOH 95:5 v/v).

2-O-desmethyl-2-O-stearoylnorquassin (3g) Compound **3g** (17.6 mg, 32 %) was prepared from norquassin (**3a**) and stearic acid using the method described for **3e**. MS (FAB) m/z (%) = 663 [$M+Na$]⁺ (88), 635 (100), 605 (5), 451 (6). ¹H NMR: δ =6.10 (d, 1H, J =2.3 Hz, C-3 H), 4.3 (m, 1H, C-7 H), 3.65 (s, 3H, C-12 OCH₃), 3.05 (m, 1H, C-15 H), 2.95 (s, 1H, C-9 H), 2.6-2.35 (m, 5H, α -CH₂, C-4 H, C-14 H, C-15 H), 2.1 (m, 2H), 1.85 (s, 3H, C-13 CH₃), 1.65 (s, 3H, C-10 CH₃), 1.3 (32H, m, 16 CH₂), 1.2 (s, 3H, C-8 CH₃), 1.15 (d, 3H, J =6.1 Hz, C-4 CH₃), 0.85 (m, 3H, CH₃). Rf=0.73; CHCl₃:MeOH; 95:5 v/v.

2-O-desmethyl-2-O-(methoxyethoxymethyl)quassin (3h) Compound **3h** (27.4 mg, 44 %) was prepared from norquassin (**3a**) and MEMCl using the method described for **3b**. MS (FAB) m/z (%) = 485 [$M+23$]⁺ (28), 413 (40), 385 (9), 353 (8), 329 (7), 301 (10), 277 (10), 247 (24), 217 (17), 199 (11), 176 (100), 149 (56), 107 (30), 95 (48). ¹H NMR (B): δ =5.85 (d, 1H, J =2.4 Hz, C-3 H), 4.8 (m, 2H, α CH), 4.4 (m, 1H, C-7 H), 3.55 (s, 3H, C-12 OCH₃), 3.4 (s, 3H, OCH₃), 2.95 (s, 1H, C-9 H), 3.1 (m, 1H, C-15 H), 2.6-2.4 (m, 2H, C-4 H, C-14 H), 2.25-1.5 (m, 2H, C-6 H, C-5 H), 1.85 (s, 3H, C-13 CH₃), 1.55 (s, 3H, C-10 CH₃), 1.25 (s, 3H, C-8 CH₃), 1.15 (d, 3H, J =6.1 Hz, C-4 CH₃).

2-O-desmethyl-2-O-[2-(tert-butoxycarbonylamino)acetyl]quassin (3i) Compound **3i** (37 mg, 33 %) was prepared from norquassin (**3a**) and *N*-(tert-butoxycarbonyl)glycine using the method described for **3e**. MS (FAB) m/z (%) = 554 [$M+23-H$]⁺ (100), 498 (69), 454 (5), 419 (6), 395 (6), 176 (16). High resolution MS: Calculated for C₂₈H₃₇O₉NNa (554.2366), Found=554.3176 ¹H NMR (A): δ = 6.15 (d, 1H J =2.4 Hz, C-3 H), 5.15 (m, 1H, NH), 4.3 (m, 1H, C-7 H), 4.15-4.0 (m, 2H, α CH₂), 3.65 (s, 3H, C-12 OCH₃), 3.1 (m, 1H, C-15 H), 2.95 (s, 1H, C-9 H), 2.65-2.4 (m, 3H, C-15 H, C-14 H, C-4 H), 2.1-1.96 (m, 3H, C-6 H, C-5 H), 1.9 (s, 3H, C-13 CH₃), 1.65 (s, 3H, C-10 CH₃), 1.45 [s, 9H, C(CH₃)₃], 1.25 (s, 3H, C-8 CH₃), 1.15 (d, 3H, J =6.1 Hz, C-4 CH₃).

2-O-desmethyl-2-O-[2-(tert-butoxycarbonylamino)-3-methylbutyl] quassin (3j) Compound **3j** (27.2 mg, 44 %) was prepared from norquassin (**3a**) and *N*-(tert-butoxycarbonyl)-L-valine using the method described for **3e**. MS (FAB) m/z (%) = 596 [$M+23-1$]⁺ (64), 580 (53), 540 (17), 524 (41), 502 (11), 458 (13), 440 (18), 413 (20), 379 (14), 358 (15), 329 (23), 289 (11), 223 (8). High resolution MS: Calculated for C₃₁H₄₃O₉NNa (596.2836), Found=596.3767. ¹H NMR (B): δ =6.13 (d, 1H, J =2.3 Hz, C-3 H), 5.05 (m, N-H), 4.4 (m, α -CH), 3.65 (s, C-12 OCH₃), 2.96 (s, 1H, C-9 H), 1.87 (s, 3H, C-13 CH₃), 1.65 (s, 3H, C-10 CH₃), 1.45 [s, 9H, C(CH₃)₃], 1.22 (s, 3H, C-8 CH₃), 1.15 (d, 3H, J =6.1 Hz, C-4 CH₃), 1.04 (d, CH₃), 0.96 (m, 3H, CH₃). Rf=0.88; CHCl₃:MeOH; 95:5 v/v.

2-O-desmethyl-2-O-[2-(tert-butoxycarbonylamino)-3-methylpentyl]quassin (3k): Compound **3k** (32.7 mg, 42 %) was prepared from norquassin (**3a**) and *N*-(tert-butoxycarbonyl)-L-isoleucine using the method described for **3e**. MS (FAB) m/z (%) = 610 [$M+23$]⁺ (10), 554 (29), 488 (4), 451 (3), 397 (23), 276 (7), 202 (7), 176 (24), 136 (11). ¹H NMR: δ =6.1 (d, 1H, J =2.3 Hz, C-3 H), 5.28 (m, 1H, N-H), 4.25 (m, 2H, α CH₂, C-7 H), 3.60 (s, 3H, C-12 OCH₃), 2.95 (m, 1H, C-15 H), 2.94 (s, 1H, C-9 H), 2.49-2.45 (m, 2H, C-4 H, C-14 H), 1.85 (s, 3H, C-13 CH₃), 1.52

(s, 3H, C-10 CH₃), 1.16 (s, 3H, C-8 CH₃), 1.12 [s, 9H, C(CH₃)₃], 1.08 (d, 3H, C-4 CH₃), 1.1 (d, 3H, J=6.1 Hz, CH₂), 0.96 (m, 3H, CH₃).

2-O-desmethyl-2-O-[2-(*tert*-butoxycarbonylamino)-3-benzyl propyloxy]quassin (3l) : Compound **3l** (21 mg, 25 %) was prepared from norquassin (**3a**) and *N*-(*tert*-butoxycarbonyl)-L-phenylalanine using the method described for **3e**. MS (FAB) *m/z* (%)=644 [M+Na]⁺ (96), 588 (24), 561 (9), 522 (3), 439 (23), 411 (100), 381 (9), 316 (13), 236 (24), 176 (59), 120 (87). ¹H NMR(B): δ=7.4-7.2 (m, 5H, aromatic-H's), 6.0 (d, 1H, J=2.3 Hz, C-3 H), 5.35 (m, 1H, N-H), 4.25 (m, 2H, αCH₂, C-7 H), 3.65 (s, 3H, C-12 OCH₃), 3.0 (s, 1H, C-9H), 2.6-2.35 (m, 3H, C-15 H, C-4 H, C-14 H), 2.2-1.5 (m, 3H, C-6 H, C-5H), 1.88 [s, 9H, C(CH₃)₃] 1.9 (s, 3H, C-13 CH₃), 1.56 (s, 3H, C-10 CH₃), 1.2 (s, 3H, C-8 CH₃), 1.11 (d, 3H J=6.1 Hz, C-4 CH₃).

2-O-desmethyl-2-O[2-(*tert*-butoxycarbonylamino)-decanoyloxy]quassin (3m) Compound **3m** (33 mg, 36%) was prepared from norquassin (**3a**) and 2-(*tert*-butoxycarbonylamino)-decanoic acid using the method described for **3e**. MS (FAB) *m/s* (%)=666 [M+23] (100), 610 (23), 545 (8), 142 (51). ¹H NMR: δ= 6.15 (d, 1H, J=2.3 Hz, C-3 H), 5.05 (m, 1H, N-H), 4.4 (m, 1H, α-CH), 3.65 (s, 3H, C-12 OCH₃), 3.0 (m, 1H), 2.95 (s, 1H, C-9 H), 2.60-2.55 (m, 2H, C-4 H, C-14H), 2.1-1.6 (m, 3H, C-6 Hs, C-5 H), 1.85 (s, 3H, C-13 CH₃) 1.65 (s, 3H, C-10 CH₃), 1.45 [s, 9H, C(CH₃)₃], 1.25 (m, 14 H, 7 CH₂), 1.25 (s, 3H, C-8 CH₃), 1.15 (d, 3H, J=6.1 Hz, C-4 CH₃), 0.85 (m, CH₃).

2-O-desmethyl-2-O-[2-(*tert*-butoxycarbonylamino)-dodecanoyloxy]quassin (3n):Compound **3n** (24.1 mg, 45%) was prepared from norquassin (**3a**) and 2-(*tert*-butoxycarbonylamino)-dodecanoic acid using the method described for **3e**. MS (FAB) *m/z* (%)=695 [M+23]⁺ (100), 639 (47), 595 (4), 567(2), 452 (3), 395 (10), 353 (4), 286 (5), 260 (10), 215 (8), 170 (49), 136 (7), 107 (6). High resolution MS: Calculated for C₃₈H₅₇O₉NNa (694.3931), Found=694.3758. ¹H NMR (B): δ=6.15 (1H, J=2.3 Hz, C-3H), 5.0 (m, 1H, N-H), 4.4 (m, 1H, α CH), 4.25 (m, 1H, C-7 H), 3.15 (s, 3H, C-12 OCH₃), 2.95 (s, 1H, C-9 H), 2.55-2.35 (m, 3H, C-4 H, C-14 H, C-15 H), 2.1-1.6 (m, 3H, C-6 Hs, C-5H), 1.85 (s, 3H, C-13 CH₃), 1.65 (s, 3H, C-10 CH₃), 1.45 [s, 9H, C(CH₃)₃], 1.25 (m, 18H, 9 CH₂), 1.20 (s, 3H, C-8 CH₃), 1.15 (d, 3H, J=6.1 Hz, C-4 CH₃), 0.85 (m, 3H, CH₃). Rf=0.91 (CHCl₃:MeOH 95:5 v/v).

2-O-desmethyl-2-O-[2-(*tert*-butoxycarbonylamino)-tetradecanoyloxy]quassin (3o):Compound **3o** (28.2 mg, 50%) was prepared from norquassin (**3a**) and 2-(*tert*-butoxycarbonylamino)-tetradecanoic acid using the method described for **3e**. MS (FAB) *m/z* (%)=723 (M+23+H)⁺ (35), 667 (8), 623 (3), 558 (3), 452 (2), 395 (37), 316 (19), 273 (76), 243 (33), 199 (100), 137 (7), 95 (9). ¹H NMR (B): δ= 6.15 (d, 1H, J=2.3 Hz, C-3H), 5.05 (m, 1H, N-H), 4.4 (m, 1H, α CH), 4.25 (m, 1H, C-7 H), 3.67 (s, 3H, C-12 OCH₃), 2.95 (s, 1H, C-9 H), 2.6-2.55 (m, 2H, C-15 H, C-4 H), 2.40 (dd, 1H, C-14 H, J=6Hz and 18 Hz), 2.1-1.5 (m, 2H, C-6 H, C-5 H), 1.85 (s, 3H, C-13 CH₃), 1.6 (s, 3H, C-10 CH₃), 1.45 [s, 9H, C(CH₃)₃], 1.25 (m, 22H, 11 CH₂), 1.2 (s, 3H, C-8 CH₃), 1.15 (d, 3H, J=6.1 Hz, C-4 CH₃), 0.85 (m, 3H, CH₃). IR: ν_{max} 3300, 2900, 2800, 1700, 1660, 1620 cm⁻¹.

2-O-desmethyl-2-O-[2-(*tert*-butoxycarbonylamino)-eicosanoyloxy]quassin (3p):Compound **3p** (29.3 mg, 35%) was prepared from norquassin (**3a**) and 2-(*tert*-butoxycarbonylamino)-eicosanoic acid using the method described for **3e**: MS (FAB) *m/z* (%)=807 [M+23]⁺ (100), 751 (44), 707 (5), 608 (3), 510 (4), 451 (6), 395 (7), 283 (30), 223 (5), 176 (13). ¹H NMR (B): δ=6.15 (d, 1H, J=2.3 Hz, C-3 H), 5.05 (t, 1H, N-H), 4.4 (m, 1H, αCH), 3.65 (s, 3H, C-12 OCH₃), 2.95 (s, 1H, C-9 H), 2.6-35 (m, C-4 H, C-14 H, C-15 H), 2.1 -1.5 (m, 2H, C-6 H, C-5), 1.85 (s, 3H, C-13 CH₃), 1.65 (s, 3H, C-10 CH₃), 1.45 [s, 9H, C(CH₃)₃], 1.25 (m, 34H, 17 CH₂), 1.1 (s, 3H, C-8 CH₃), 1.1 (d, 3 H,

J=6.1 Hz, C-4 CH₃), 0.89 (m, 3H, CH₃).

2,12-dihydroxypicrasa-2,12-diene-1,11,16-trione (3r): To a solution of quassin (1) (39 mg, 1.01 mg) in dry CH₂Cl₂ (15 ml) a solution of 1 M BBr₃ in CH₂Cl₂ (4 ml) was added at -78 °C and the reaction mixture stirred for 20 min. The mixture was poured into water (20 ml) and the organic layer separated. The aqueous layer was extracted with CH₂Cl₂ (2x10 ml) and the combined organic extract washed with brine, dried (MgSO₄), and concentrated. Recrystallisation from ethanol afforded 15 mg, (41%) of compound 3r as colourless prisms, which gave a grey-black colour reaction with ferric chloride. MS (EI) m/z (%)=360 [M]⁺ (100), 345 (86), 327 (10), 317 (27), 299 (24), 271 (17), 257 (16), 231 (16), 203 (19), 193 (26), 165 (35), 151 (35), 138 (39), 121 (22), 105 (24), 91 (42), 83 (57), 77 (25). ¹H NMR: δ=6.15 (s, 1H, C-2 OH), 5.75 (d, 1H, J=2.3 Hz, C-3 H), 4.35 (m, 1H, C-7 H), 2.95 (dd, J=6Hz and 18 Hz, 1H, C-15 H), 2.55 (m, 1H, C-4 CH₃), 2.4 (dd, J=6Hz and 18 Hz, 1H, C-14 H), 2.5-1.5 (m, 4H, C-5 H, C-6 Hs, C-15 H), 1.85 (s, 3H, C-13 CH₃), 1.55 (s, 3H, C-10 CH₃), 1.2 (s, 3H, C-8 CH₃), 1.1 (d, 3H, J=6.1 Hz, C-4 CH₃). Rf=0.42 (CHCl₃:MeOH 95:5 v/v).

2-Acetyloxy-12-hydroxypicrasa-2,12-diene-1,11,16-trione (3s): 2-acetyloxyquassin (3b) was reacted as described for 3r to yield 14.6 mg (50%) 3s. MS (EI) m/z (%)=402 [M]⁺ (22), 387 (11), 374 (12), 360 (100), 345 (87), 317 (34), 271 (15), 255 (13), 231 (16), 215 (10), 203 (12), 193 (20), 151 (21), 138 (25), 105 (17), 91 (37), 77 (27). ¹H NMR: δ=6.15 (d, 1H, J=2.4 Hz, C-3 H), 4.3 (m, 1H, C-7 H), 3.0 (s, 1H, C-9 H), 3.1 (m, 1H, C-15 H), 2.5 (m, 1H, C-4 H), 2.2 (s, COCH₃), 1.9 (s, 3H, C-13 CH₃), 1.65 (s, 3H, C-10 CH₃), 1.3 (s, 3H, C-8 CH₃), 1.1 (d, 3H, J=6.1 Hz, C-4 CH₃).

2-benzoyl-12-hydroxypicrasa-2,12-diene-1,11,16-trione (3t): Compound 3c was reacted as described for 3r to yield 14.8 mg (38%) 3t. MS (EI) m/z (%)=464 [M]⁺ (100), 449 (5), 378 (5), 360 (100), 345 (97), 327 (15), 327 (15), 317 (53), 299 (47), 271 (28), 255 (26), 239 (33), 215 (28), 203 (33), 195 (74), 175 (35). ¹H NMR (B): δ=8.13-7.48 (m, 5H, aromatic-H's), 6.25 (d, 1H, J=2.3 Hz, C-3 H), 5.74 (m, 1H, C-12 OH), 4.2 (m, 1H, C-7 H), 3.03 (s, 1H, C-9 H), 2.50-2.40 (m, 2H, C-4/C-14 H), 1.88 (s, 3H, C-13 CH₃), 1.70 (s, 3H, C-10 CH₃), 1.25 (s, 3H, C-8 CH₃), 1.1 (d, 3H, J=6.1 Hz, C-4 CH₃).

15β-(3,4-dimethylacryloxy)quassin (4b): Hydroxyquassin (4a) and 3,3-dimethylacryloyl chloride was reacted as described for 3b to afford 14 mg (58%) of 4b. High resolution MS: Calculated for C₂₇H₃₄O₈ (486.2254), Found=486.2250. ¹H NMR (B): δ=5.79 (s, 1H, C-2' H), 5.3 (d, 1H, J=2.4 Hz, C-3 H), 5.16 (d, 1H, J=10.2 Hz, C-15 H), 4.5 (m, 1H, C-7 H), 3.69 (s, 3H, C-12 OCH₃), 3.59 (s, 3H, C-2 OCH₃), 3.05 (s, 1H, C-9 H), 2.39 (d, 1H, J=10.2 Hz, C-14 H), 2.48 (m, 1H, C-4 H), 2.21 (s, 3H, C-5'CH₃), 1.96 (s, 3H, C-4' CH₃), 1.92 (s, 3H, C-13 CH₃), 1.54 (s, 3H, C-10 CH₃), 1.21 (s, 3H, C-8 CH₃), 1.12 (d, 3H, J=6.1 Hz, C-4 CH₃). Rf=0.89 (CHCl₃:MeOH 95:5 v/v).

15β-acetyloxyquassin (4c): Hydroxyquassin (4a) and acetic anhydride was reacted as described for 3f to afford 27 mg (61%) of 4c: High resolution MS: Calculated for C₂₄H₃₀O₈ (446.1941), Found=446.1947. MS (EI) m/z (%)=446 [M]⁺ (8), 404 (4), 386 (94), 371 (86), 353 (25), 343 (31), 329 (19), 315 (17), 301 (18), 283 (15), 269 (15), 255 (14), 205 (25), 165 (46), 151 (28), 121 (29), 105 (34), 94 (100), 77 (54). ¹H NMR: δ=5.35 (d, 1H, J=2.5 Hz, C-3 H), 5.25 (d, 1H, J=10.5 Hz, C-15 H), 4.5 (m, 1H, C-7 H), 3.7 (s, 3H, C-12 OCH₃), 3.6 (s, 3H, C-2 OCH₃), 3.1 (s, 1H, C-9 H), 2.6 (d, 1H, J=10.5 Hz, C-14 H), 2.45 (m, 1H, C-4 H), 2.2 (s, 3H, COCH₃), 2.15-1.6 (m, 3 H,

C-5 H, C-6 Hs), 1.95 (s, 3H, C-13 CH₃), 1.5 (s, 3H, C-10 CH₃), 1.2 (s, 3H, C-8 CH₃), 1.1 (d, 3H, J=6.1 Hz, C-4 CH₃). Rf=0.62 (CHCl₃:MeOH 95:5 v/v).

15β-[(2-tert butoxycarbonylamino)-decanoyloxy]quassin (4d): Compound **4d** (22 mg, (33%) was prepared from hydroxyquassin (**4a**) and *N*-(*tert*-butoxycarbonyl-amino)-decanoic acid- using the method described for **3e**. MS (FAB) m/z (%)=696 [M+Na]⁺ (45), 640 (50), 425 (11), 395 (20), 332 (14), 186 (21), 142 (100). ¹H NMR (A): δ=5.3 (d, 1H, J=2.4 Hz, C-3 H), 5.0 (m, 1H, N-H), 4.95 (d, 1H, J=10.6 Hz, C-15 H), 4.55 (m, 1H, α-CH), 4.35 (m, 1H, C-7 H), 3.65 (s, 3H, C-12 OCH₃), 3.55 (s, 3H, C-2 OCH₃), 2.95 (s, 1H, C-9 H), 2.6 (d, 1H, J=10.6 Hz, C-14 H), 2.35 (m, 1H, C-4 H), 2.10-1.5 (m, 3H, C-5 H, C-6 Hs), 1.95 (s, 3H, C-13 CH₃), 1.5 (s, 3H, C-10 CH₃), 1.4 [s, 9H, C(CH₃)₃], 1.2 (s, 14H, 7 CH₂), 1.1 (s, 3H, C-8 CH₃), 1.05 (d, 3H, J=6.1 Hz, C-4 CH₃), 0.8 (m, 3H, CH₃).

15β-(methoxyethoxymethoxy)quassin (4e): Hydroxyquassin (**4a**) and methoxyethoxymethyl chloride was reacted as described for **3b** to afford 11.3 mg (46%) of **4e** as a colourless oil. MS (EI) m/z (%)=493 [M]⁺ (26), 416 (26), 403 (75), 386 (37), 371 (18), 329 (100), 315 (17), 297 (17), 269 (32), 255 (24), 203 (31), 185 (35), 165 (76), 151 (39). ¹H NMR: δ=5.25 (d, 1H, J=2.4 Hz, C-3 H), 4.6 (m, 2H, CH₂), 4.5 (d, 1H, J=10.6 Hz, C-15 H), 3.8 (m, 2H, CH₂), 3.7 (m, 2H, CH₂), 3.65 (s, 3H, C-12 OCH₃), 3.59 (s, 3H, C-2 OCH₃), 3.4 (s, 3H, OCH₃), 3.06 (s, 1H, C-9 H), 2.50 (m, 1H, C-4 H), 2.35 (d, 1H, J=10.6 Hz, C-14), 2.08 (s, 3H, C-13 CH₃), 1.54 (s, 3H, C-10 CH₃), 1.25 (s, 3H, C-8 CH₃), 1.13 (d, 3H, J=6.1 Hz, C-4 CH₃). Rf=0.76 (CHCl₃:MeOH 95:5 v/v).

2,15β-dihydroxy-12-methoxypicrasa-2,12-diene-1,11,16-trione (4f): A mixture of hydroxyquassin **4a** (50 mg, 1.24 mmol), 10 % HCl (15 ml), and AcOH (4 ml) was refluxed for 2 hours. The mixture was neutralised with 2M NaOH at room temperature, extracted with CH₂Cl₂ (3x15 ml), washed with brine, dried (MgSO₄), and concentrated. The residue was purified by (CH₂Cl₂:MeOH 95:5 v/v) and recrystallised from ethanol to afford 35 mg (73%) of **4f** as colourless prisms which gave a grey-black colour with ferric chloride. MS (EI) m/z (%)= 390 [M]⁺ (100), 376 (7), 361 (9), 316 (69), 301 (32), 283 (9), 273 (14), 245 (6), 231 (13), 203 (7), 165 (12), 151 (7), 137 (7), 83 (33), 69 (31). ¹H NMR (A): δ=5.7 (d, 1H, J=2.4 Hz, C-3 H), 5.5 (s, 1H, C-2 OH), 4.5 (d, 1H, J=10.6 Hz, C-15 H), 4.4 (m, 1H, C-7 H), 3.7 (s, 3H, C-12 OCH₃), 3.2 (s, 1H, C-9 H), 2.5 (m, 1H, C-4 H), 2.4 (d, 1H, J=10.6 Hz, C-14 H), 2.1-1.5 (m, 3H, C-5, C-6 Hs), 2.1 (s, 3H, C-13 CH₃), 1.5 (s, 3H, C-10 CH₃), 1.2 (s, 3H, C-8 CH₃), 1.1 (d, 3H, J=6.1 Hz, C-4 CH₃).

2-O-desmethyl-2-O-[(2-tert butoxycarbonylamino)-decanoyloxy]hydroxyquassin (4g): Compound **4g** (17 mg, 21%) was prepared from **4f** and *N*-(*tert*-butoxycarbonyl-amino)-decanoic acid using the method described for **3e**. The compound gave negative ferric chloride reaction. MS (FAB) m/z (%)=682 [M+23-1]⁺ (100), 626 (39), 582 (3), 413 (14), 258 (6), 232 (8), 176 (45), 142 (35). High resolution MS: Calculated for C₃₆H₅₃O₇NNa (682.3567), Found=682.2808. ¹H NMR (B): δ=6.13 (d, 1H, J=2.3 Hz, C-3 H), 5.02 (m, 1H, N-H), 4.50 (d, 1H, J=10.7 Hz, C-15H), 4.48 (m, 1H, C-2'H), 4.44 (m, 1H, C-7 H), 3.68 (s, 3H, C-12 OCH₃), 3.29 (bs, 1H, C-15 OH), 3.02 (s, 1H, C-9 H), 2.56 (m, 1H, C-4 H), 2.36 (d, 1H, J=10.7 Hz, C-14 H), 2.08 (s, C-13 CH₃), 1.92 (m, 3H, C-6 H, C-5 H), 1.43 [s, 9H, C(CH₃)₃], 1.43 (s, 3H, C-10 CH₃), 1.25 (m, 14 H, 7 CH₂), 1.15 (d, 3H, J=6.1 Hz, C-4 CH₃), 0.86 (m, 3H, CH₃). Rf=0.75 (CHCl₃:MeOH 95:5 v/v).

2-O-desmethyl-2-O-(3,3-dimethylacrylyl)-15β-(3,3-dimethylacryloxy)quassin (4h): Norhydroxyquassin **4f** and 3,3-dimethylacryloyl chloride were reacted as described for compound **3b** to afford 30 mg (53%) of **4h**. MS (CI)

m/z (%)=577 $[M+23]^+$ (30), 555 $(M+H)^+$ (86), 528 (14), 513 (7), 473 (20), 455 (29), 413 (7), 391 (8), 373 (26), 118 (15), 100 (16), 83 (100). High resolution MS: Calculated for $C_{31}H_{38}O_9Na$ (577.2414), Found= 577.3048. 1H NMR (B): δ =6.1 (d, 2H, 1H, C-3H), 5.8 (m, 2H, C-2'CH), 5.1 (d, 1H, J =10.6 Hz, C-15H), 4.55 (m, 1H, C-7H), 3.65 (s, 3H, C-12 OCH_3), 3.01 (s, 1H, C-9 H), 2.56 (d, 1H, J =10.6 Hz, C-14 H), 2.5 (m, 1H, C-4 H), 2.2 (s, 3H, C-5' CH_3), 2.15 (s, 3H, C-5' CH_3), 2.0 (s, 3H, C-4' CH_3), 1.95 (s, 3 H, C-4' CH_3), 1.9 (s, 3H, C-13 CH_3), 1.6 (s, 3H, C-10 CH_3), 1.25 (s, 3H, C-8 CH_3), 1.15 (d, 3H, J =6.1 Hz, C-4 CH_3). Rf=0.92 ($CHCl_3$:MeOH; 95:5).

2,12-dihydroxy-15 β -(3,3-dimethylacryloxy)-picrasa-2,12-diene-1,11,16-trione (4i): Hydroxyquassin 4a and 3,3-dimethylacryloyl chloride were reacted as described for compound 3b to afford 5.6 mg (27 %) of compound 4i, which gave a grey-black colour ferric chloride reaction. MS (FAB) m/z (%)= 481 $[M+23]^+$ (36), 413 (33), 383 (6), 357 (3), 326 (6), 301 (9), 199 (13), 176 (100), 154 (285), 136 (27), 107 (19). 1H NMR (A): δ =5.79 (s, 1H, C-2' H), 5.74 (m, 1H, C-3 H), 5.16 (d, 1H, J =10.2 Hz, C-15 H), 4.52 (m, 1H, C-7 H), 3.11 (s, 1 H, C-9 H), 2.70 (1H, m, C-4H), 2.65 (d, 1H, J =10.6 Hz, C-14H), 2.21 (s, 3H, C-5' CH_3), 1.96 (s, 3H, C-4' CH_3), 1.96 (s, 3H, C-13 CH_3), 1.52 (s, 3H, C-10 CH_3), 1.24 (s, 3H, C-8 CH_3), 1.12 (d, 3H, J =6.1 Hz, C-4 H).

2,12-di-O-desmethyl-15-hydroxyquassin (4j): Hydroxyquassin 4a was reacted as described for compound to give 30 mg (50%) of ferric chloride positive compound 4j. Recrystallisation from ethanol gave colourless prisms. MS (EI) m/z (%)=376 $[M]^+$ (44), 361 (3), 330 (7), 315 (13), 301 (100), 287 (18), 273 (14), 259 (8), 231 (8), 215 (9), 192 (12), 165 (12), 151 (19), 137 (10), 105 (7), 91 (12), 77 (9), 69 (59), 55 (8). 1H NMR (A): δ =6.2 (s, 1H, C-12 OH), 5.7 (d, 1H, J =2.4 Hz, C-3 H), 5.6 (s, 1H, C-2 OH), 4.5 (d, 1H, J =10.2 Hz, C-15 H), 4.4 (m, 1H, C-7 H), 3.1 (s, 1H, C-9 H), 2.5 (m, 1H, C-4 H), 2.4 (d, 1H, J =10.2 Hz, C-14 H), 2.2-1.8 (m, 3H, C-5H, C-6 H), 2.1 (s, 3H, C-13 CH_3), 1.5 (s, 3H, C-10 CH_3), 1.2 (s, 3H, C-8 CH_3), 1.1 (d, 3H, J =6.1 Hz, C-4 CH_3). U.V. (MeOH) λ =274 nm

2,12-di-O-desmethyl-2-O-[(2-*tert*-butoxycarbonylamino)-decanoyl]-15-hydroxyquassin (4k)

2,12,15-Trihydroxyquassin 4j and 2-(*tert*-butoxycarbonyl-amino)-decanoic acid were reacted as described for compound 3e to yield 12.6 mg (21%) of 4k. MS (FAB) m/z (%)=668+23-1 $^+$ (37), 613 (13), 186 (10), 142 (100), 95 (36). High resolution MS: Calculated for $C_{35}H_{51}O_{10}NNa$ (668.3411), Found=668.3766. 1H NMR (B): δ =6.5 (d, 1H, J =2.4 Hz, C-3 H), 6.15 (s, 1H, C-12 OH), 5.0 (m, 1H, N-H), 4.45 (d, 1-H, J =10.7 Hz, C-15 H), 4.4 (m, 1H, C-2' H), 4.35 (m, 1H, C-7 H), 3.2 (s, 1H, C-15 OH), 3.1 (s, 1H, C-9 H), 2.6 (m, 1H, C-4 H), 2.38 (d, 1H, J =10.7 Hz), 2.05 (s, 3H, C-13 CH_3), 1.55 (s, 3 H, C-10 CH_3), 1.45 [m, 9H, C(CH_3) $_3$], 1.25 (m, 14H, 7 CH_2), 1.20 (s, 3H, C-8 CH_3), 1.15 (d, 3H, J =6.1 Hz, C-4 CH_3), 0.85 (m, 3H, CH_3). Rf=0.80 ($CHCl_3$:MeOH 95:5 v/v).

2,12-di-O-desmethyl-2,12-di-O-acetyl-15-acetyloxyquassin (4l): Compound 4j was reacted with acetic anhydride as described for compound 3f to yield 21 mg (45%) of 4l. MS (CI) m/z (%)=525 $[M+23]^+$ (100), 503 $[M]^+$ (28), 478 (8), 460 (25), 443 (15), 418 (6), 391 (11), 343 (6), 279 (6), 198 (4), 151 (3), 120 (4). High resolution MS: Calculated for $C_{26}H_{30}O_{10}Na$ (525.1737), Found= 525.2489. 1H NMR (B): δ =6.1 (d, 1H, J =2.4 Hz, C-3 H), 5.25 (d, 1H, J =10.8 Hz, C-15 H), 4.5 (m, 1H, C-7 H), 3.1 (s, C-9 H), 2.7 (d, 1H, J =10.8 Hz, C-14 H), 2.55 (t, 1H, C-4 H), 2.25 (s, 3H, C-12 $COCH_3$), 2.2 (s, 3H, C-2 $COCH_3$), 2.15 (s, 3H, C-15 $COCH_3$), 2.1-1.85 (m, 3H, C-6 Hs, C-5 H), 1.85 (s, C-13 CH_3), 1.6 (s, 3H, C-10 CH_3), 1.4 (s, 3H, C-8 CH_3), 1.15 (d, 3H, J =6.1 Hz, C- CH_3). Rf=0.84 ($CHCl_3$:MeOH 95:5 v/v).

2,12-di-O-desmethyl-2,12-di-O-hexanoyl-15-hexanoyloxyquassin (4m): Compound 4j was reacted with

hexanoic anhydride as described for compound **3f** to afford 9.3 mg (21%) **4m**. MS (FAB) m/z (%)=671 [M+1]⁺ (100), 646 (9), 605 (13), 573 (33), 559 (10), 527 (13), 489 (8), 463 (10), 391 (24), 359 (13), 302 (16), 279 (36), 206 (9). ¹H NMR (A): δ =6.07 (d, 1H, J=2.4 Hz, C-3 H), 5.15 (d, 1H, J=10.7 Hz, C-15 H), 4.55 (m, 1H, C-7 H), 3.05 (s, 1H, C-9 H), 2.7 (d, 1H, J=10.7 Hz, C-14 H), 2.55-2.49 (m, 7H, C-4 H, α CH₂), 2.2-1.6 (m, 3H, C-6 Hs, C-5 H), 1.85 (s, 3H, C-13 CH₃), 1.57 (s, 3H, C-10 CH₃), 1.37 (s, 3H, C-8 CH₃), 1.16 (d, 3H, J=6.1 Hz, C-4 CH₃), 0.91 (m, 9H, 3 CH₃).

2,12-di-O-desmethyl-2,12-di-O-stearoyl-15 stearoyloxyquassin (4n) Compound **4j** was reacted with stearic acid as described for compound **3e** to yield 18 mg (28%) of tristearate **4n**. MS: (FAB) m/z (%) =1197 [M+23]⁺ (20), 1181 (14), 1169 (100), 1156 (18), 143 (98), 1128 (18), 1114 (63), 1097 (13), 1084 (13), 1068 (11), 1056 (17), 1042 (15), 1028 (14), 1014 (14). ¹H NMR (B) δ =6.1 (d, 1H, J=2.3 Hz, C-3 H), 5.2 (d, 1H, J=10.6 Hz, C-15 H), 4.6 (m, 1H, C-7 H), 3.15 (s, 1H, C-9 H), 2.75 (d, 1H, J=10.6 Hz, C-14 H), 2.65-2.4 (m, 7H, 3 α -CH₂, C-4 H), 2.2-1.5 (m, 3H, C-6 Hs, C-5 H), 1.89 (s, C-13 CH₃), 1.62 (s, 3H, C-10 CH₃), 1.41 (s, C-8 CH₃), 1.20 (d, 3H, J=6.1 Hz, C-4 CH₃), 0.90 (m, 9H, 3 CH₃). Rf=0.93 (CHCl₃:MeOH 95:5 v/v).

2,15 β -di(3,3-acryloxy)-16-hydroxy-12-methoxypicrasa-2,12-diene-1,11-dione (5): To a solution of **4h** (8.6 mg, 0.015 mmol) in ethanol/ chloroform (2 ml, 11ml) NaBH₄ (10 mg) was added and the reaction mixture stirred at room temperature for 30 min. The mixture was diluted with CHCl₃ (5 ml), washed with brine, the organic phase dried (Na₂SO₄) and concentrated to yield 7.5 mg (87%) of **5** as a diastereomeric mixture. MS (FAB) m/z (%)=557 [M+1]⁺ (27), 541 (47), 499 (100), 484 (20), 457 (21), 415 (48), 391 (94), 373 (8), 355 (13), 331 (14), 307 (34), 289 (40), 279 (19), 269 (14), 241 (20), 219 (33). High resolution MS: Calculated for C₃₁H₄₀O₉Na (579.2570), Found= 579.3464. ¹H NMR (B): δ =6.08 (d, 1H, J=2.4 Hz, C-3 H), 5.81 (s, 1H, C-2'H), 5.7 (s, 1H, C-2'H), 5.42 (m, 0.5H, C-16 H), 5.23 (dd, 0.5H, J=11.3 and 3.4 Hz, C-15 H), 5.07 (m, 0.5H, C-15 H), 4.6 (m, 0.5H, C-16 H), 4.04 (m, 0.5H, C-7 H), 3.65 (s, 3H, C-12 OCH₃), 3.27 (s, 1H, C-9 H), 2.53 (d, 1H, J=11.3 Hz, C-14 H), 2.51 (m, 1H, C-4 H), 2.20 (s, 3H, C-5' CH₃), 2.19 (s, 3H, C-5' CH₃), 1.94 (s, 3H, C-4' CH₃), 1.93 (s, 3H, C-4' CH₃), 1.93 (s, 3H, C-13 H), 1.60 (s, 3H, C-10 CH₃), 1.25 (s, 3H, C-8 CH₃), 1.11 (d, 3H, J=6.1 Hz, C-4 CH₃).

2-desmethyl-2-[2-(tert-butoxycarbonylamino)-3-methylbutyloxy]neoquassin (6a): Compound **3j** was reduced using the procedure described for compound **5** to yield 10 mg (66%) of **6a** as a diastereomeric mixture. MS (FAB) m/z (%)=599 [M+Na+1]⁺ (100), 581 (14), 542 (18), 526 (7), 458 (8), 377 (6), 329 (12), 272 (9), 207 (7), 176 (54), 154 (49), 136 (30), 116 (21). High resolution MS: Calculated for C₃₁H₄₅O₉NNa (598.2992), Found= 598.3852. ¹H NMR (B): δ =6.03 (d, 1H, J=2.4 Hz, C-3 H), 5.31 (d, 0.5H, J=2.4 Hz, C-16 H), 5.0 (m, 1H, NH), 4.8 (m, 0.5H, C-16 H), 4.33 (m, 0.5H, α -CH), 4.30 (m, 0.5H, α -CH), 3.8 (t, 1H, C-7 H), 3.55 (s, 3H, C-12 OCH₃), 3.09 (s, 0.5H, C-9 H), 3.08 (s, 1H, C-9 H), 2.5 (m, 1H, C-4 H), 1.79 (s, 3H, C-13 CH₃), 1.54 (s, 3H, C-10 CH₃), 1.37 [s, 9H, C(CH₃)₃], 1.22 (s, 3H, C-8 CH₃), 1.14 (d, 3H, J=6.1 Hz, C-4 CH₃), 0.99 (m, 3H, CH₃), 0.87 (m, 3H, CH₃). Rf=0.77 (CHCl₃:MeOH 95:5 v/v).

2-desmethyl-2-[2-(tert-butoxycarbonylamino)tetradecanoyloxy]neoquassin (6b): Compound **3o** was reduced using the procedure described for compound **5** to yield 11 mg (73%) of **6b**. MS (FAB) m/z (%)=725 [M+23]⁺ (54), 707 (11), 669 (8), 651 (7), 599 (5), 394 (82), 316 (36), 272 (94), 242 (38), 198 (100), 176 (32), 154 (26), 154 (26), 136 (17). ¹H NMR (B): δ =6.1 (d, 1H, J=2.4 Hz, C-3 H), 5.39 (m, 1H, C-16 H), 5.0 (m, 1H, NH), 4.4 (m, 1H, α -CH), 3.9 (m, 1H, C-7 H), 3.7 (s, 3H, C-12 OCH₃), 3.13 (s, 1H, C-9 H), 2.51 (m, 1H, C-4 H), 1.85 (s, 3H, C-13 CH₃),

1.6 (s, 3H, C-10 CH₃), 1.45 [s, 9H, C(CH₃)₃], 1.25 (m, 18H, 9 CH₂), 1.09 (s, 3H, C-8 CH₃), 1.06 (d, 3H, J=6.1 Hz, 4-C CH₃), 0.89 (m, 3H, CH₃).

2,12,16-trimethoxypicrasa-2,12,-diene-1,11-dione (7): To a solution of quassin 1 (2.8 g) in abs. ethanol (400 ml) 1 equivalent of NaBH₄ was added and the mixture was stirred for 2.5 h at room temperature. A few drops of acetic acid was added to destroy NaBH₄ and the solvent was evaporated to give a white residue. The residue was placed in water, extracted with CH₂Cl₂ (4x35 ml) and the combined organic extracts washed with brine (50 ml), dried (MgSO₄), and concentrated *in vacuo* to yield the hemiacetal, neoquassin which was used without further purification. To a solution of neoquassin (2.4 g, 6.15 mmol), in methanol (30 ml), conc. HCl (2 ml) was added and the reaction mixture stirred at room temperature for 5 h. The mixture was poured into a solution of saturated aqueous NaHCO₃ (30 ml) and extracted with CHCl₃ (3x25 ml). The combined organic extracts were washed with brine (20 ml), dried (Na₂SO₄) and concentrated. The residue was purified by tlc (ethyl acetate 100%) to afford 2.15g (86%) of 7. MS (EI) m/z (%)=404 [M]⁺ (100%), 389 (22), 372 (18), 357 (13), 329 (23), 302 (37), 212 (32), 152 (80), 127 (32), 105 (24), 91 (38), 69 (82), 55 (37). ¹H NMR (A): δ=5.28 (d, 1H, J=2.4 Hz, C-3 H), 4.8 (m, 1H, C-16 H), 3.62 (m, 1H, C-7 H), 3.7 (s, 3H, OCH₃), 3.6 (s, 3H, C-2 OCH₃), 3.35 (s, C-16 OCH₃), 3.2 (s, 1H, C-9 H), 2.4 (m, 1H, C-4 H), 2.1-1.2 (m, 3H, C-6 Hs, C-5 H), 1.85 (s, 3H, C-13 CH₃), 1.55 (s, 3H, C-10 CH₃), 1.2 (d, 3H, J=6.1 Hz, C-4 CH₃), 1.15 (s, C-8 CH₃).

1β-hydroxy-2,12,16-trimethoxypicrasa-2,12,-diene-11-one (8): To a solution of 7 (2.0 g, 4.95 mmol), in abs. ethanol, CeCl₃·7H₂O (1.9 mg, 5.09 mmol) was added and the reaction mixture stirred for 15 min at room temperature. The mixture was cooled (-5°C) and a solution of NaBH₄ (200 mg) in abs. ethanol (15 ml) was added and the mixture stirred for 1 h. The reaction was quenched with acetone and the solvents evaporated. The residue was dissolved in CHCl₃ (50 ml), washed with saturated NaHCO₃ (20 ml), brine (20 ml), dried (MgSO₄) and concentrated. The crude compound was purified by tlc (ethyl acetate: hexane 3:1) to yielded 1.62 g (81%) of 8. MS (EI) m/z (%)=406 [M]⁺ (9), 391 (8), 375 (81), 359 (14), 343 (13), 327 (6), 315 (6), 299 (7), 212 (23), 179 (14), 165 (16), 152 (32), 94 (89), 69 (35), 55 (54), 43 (100). ¹H NMR (500 MHz): δ=6.71 (s, 1H, OH), 4.83 (m, 1H, C-16 H), 4.51 (s, 1H, C-1 H), 4.03 (m, 1H, C-3 H), 3.65 (m, 1H, C-7 H), 3.63 (s, 3H, C-12 OCH₃), 3.56 (s, 3H, C-2 OCH₃), 3.38 (s, 3H, C-16 OCH₃), 2.89 (s, 1H, C-9 H), 2.36-2.15 (m, 3H, C-15 H, C-4 H, C-14 H), 2.04 (s, 3H, C-13 CH₃), 1.15 (s, 3H, C-10 OCH₃), 1.1 (s, 3H, C-8 CH₃), 1.01 (d, 3H, J=6.1 Hz, C-4 CH₃).

1β-hydroxy-12,16-dimethoxypicras-12-ene-2,11-dione (9): A mixture of 8 (800 mg, 1.97 mmol), and pyridinium toluene sulphonate (240 mg, 0.95 mmol) in actone (20 ml), and water (2.6 ml) was refluxed for 3 hours. The mixture was cooled and concentrated. The residue was dissolved in CH₂Cl₂ (50 ml), washed with saturated aqueous NaHCO₃ (20 ml), brine (20 ml), dried (Na₂SO₄), and concentrated. Purification of the crude product by tlc (ethyl acetate-hexane 3:1) afforded 550 mg, (71%) of 9. MS (EI) m/z (%)=392 [M]⁺ (12), 360 (9), 331 (6), 317 (7), 287 (9), 245 (11), 212 (58), 179 (28), 165 (32), 152 (100), 137 (27), 105 (27), 91 (47), 77 (40), 69 (65), 55 (72), 43 (85), 29 (24). ¹H NMR (500 MHz): δ=4.9 (m, 1H, C-16 H), 4.01 (s, 1H, C-1 H), 3.65 (m, 1H, C-7H), 3.58 (s, 3H, C-12 OCH₃), 3.36 (s, 3H, C-16 OCH₃), 3.11 (s, 1H, C-9 H), 2.3-1.5 (m, 6H, C-3 H, C-4 H, C-5 H, C-6 H, C-14 H, C-15 H), 1.85 (s, C-13 CH₃), 1.04 (s, 3H, C-10 CH₃), 1.03 (s, 3H, C-8 CH₃), 1.01 (d, 3H, J=6.1 Hz, C-4 CH₃). IR: ν_{max} =3400, 1730, 1700, 1670 cm⁻¹.

1β-Acetyloxy-12,16-dimethoxypicras-12-ene-2,11-dione (10): To a solution of 9 (500 mg, 1.27 mmol) and

DMAP (200 mg, 1.63 mmol) in CHCl_3 (5ml), acetic anhydride (3 ml) was added and the mixture stirred for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 (10 ml), washed with saturated aqueous NaHCO_3 (10 ml), brine (10 ml), dried (Na_2SO_4) and concentrated. The residue was purified by tlc (ethyl acetate-hexane 3:1) to yield 306 mg (55%) of **10**. MS (EI) m/z (%)=434 $[\text{M}]^+$ (16), 404 (29), 392 (42), 374 (7), 302 (12), 271 (14), 212 (35), 179 (25), 165 (28), 152 (100), 137 (28), 121 (84), 105 (28), 91 (47), 83 (62), 69 (56), 55 (51). ^1H NMR (B): δ =5.1 (s, 1H, C-1 H), 4.9 (m, 1H, C-16 H), 3.65 (m, 1H, C-7 H), 3.5 (s, 3H, C-12 OCH_3), 3.0 (s, 1H, C-9 H), 2.5 (m, 1H, C-15 H), 2.3-1.5 (m, 6H, C-15 H, C-14 H, C-6 Hs, C-5 H, C-4 H), 2.2 (s, 3H, C-1 COCH_3), 1.75 (s, 3H, C-13 CH_3), 1.4 (s, 3H, C-10 CH_3), 1.1 (s, 3H, C-8 CH_3), 1.05 (d, 3H, J =6.1 Hz, C-4 CH_3).

1 β -acetyloxy-16-hydroxy-12-methoxypicras-12-ene-2,11-dione (11): A solution of **10** (100 mg, 0.23 mmol) in THF (2 ml) and 10% HCl (2ml) was stirred at room temperature for 10 h. The mixture was poured into a cool (0°C) solution of saturated NaHCO_3 (5 ml), and solid NaHCO_3 added until no bubbles were seen. The mixture was extracted with diethyl ether (3x10 ml), dried (NaSO_4), and concentrated. Purification of the residue by tlc (ethyl acetate-hexane 75:25) yielded 73 mg (75%) of **11**. MS (FAB) m/z (%)=443 $[\text{M}+\text{Na}]^+$ (83), 429 (58), 413 (75), 401 (27), 379 (33), 361 (7), 329 (87), 307 (21), 289 (26), 273 (7), 219 (50). H^1 NMR (B): δ =5.0 (s, 1H, C-1 H), 4.8 (m, 1H, C-16 H), 3.90 (m, 1H, C-7 H), 3.55 (s, 3H, C-12 OCH_3), 3.0 (s, 1H, C-9 H), 2.4 (m, 1H, C-14 H), 2.2-1.5 (m, 3H, C-15 H, C-6H, C-5H), 2.1 (s, 3H, C-1 COCH_3), 1.8 (s, 3H, C-13 CH_3), 1.5 (s, 3H, C-10 CH_3), 1.3 (s, C-8, CH_3), 1.0 (d, 3H, J =6.1 Hz, C-4 CH_3).

1 β -acetyloxy-12-methoxypicras-12-ene-2,11,16-trione (12): To a solution of lactol **11** (73 mg, 0.174 mmol) in CH_2Cl_2 (4 ml) pyridinium chlorochromate (260 mg, 1.2 mmol) was added and mixture stirred at room temperature for 2 h. The reaction mixture was diluted with diethyl ether and filtered through a pad of flash silica gel. The filtrate was concentrated and the residue purified by column chromatography (100% CHCl_3) to give 32.2 mg (44%) of lactone **12**. MS (FAB) m/z (%)=441 $[\text{M}+23]^+$ (27), 413 (69), 391 (14), 329 (6), 259 (4), 219 (3), 176 (35), 149 (100). ^1H NMR (B): δ =5.1 (s, 1H, C-1 H), 4.3 (m, 1H, C-7H), 3.55 (s, 3H, C-12 OCH_3), 3.01 (dd, J =6Hz and 18 Hz, 1H, C-15 H), 2.85 (s, 1H, C-9 H), 2.6-2.4 (m, 3H, C-4 H, C-14 H, C-15 H), 2.2-1.6 (m, 4H, C-6 Hs, C-5 H, C-3 H), 2.1 (s, 3H, C-1 COCH_3), 1.84 (s, 3 H, C-13 CH_3), 1.43 (s, 3H, C-10 CH_3), 1.17 (s, 3H, C-8 CH_3), 1.05 (d, 3H, J =6.1 Hz, C-4 CH_3).

1 β -acetyloxy-16-ethoxy-12-methoxypicras-12-ene-2,11-dione (13): The compound was prepared by an identical way as compound **10**, using ethanol for the introduction of C-16 ethoxy group. MS (EI) m/z (%)=449 $[\text{M}+\text{H}]^+$ (21), 435 (11), 421 (9), 407 (100), 393 (23), 375 (10), 361 (14), 345(13), 317 (11), 287 (13), 274 (11), 245 (14), 217 (15), 207 (18). High resolution MS Calculated for $\text{C}_{25}\text{H}_{37}\text{O}_7$ (449.2539), Found=449.2535. ^1H NMR (B): δ =5.11 (s, 1H, C-1 H), 4.98 (m, 1H, C-16 H), 3.74 (m, 1H, C-16 OCH_2), 3.71 (m, 1H, C-7 H), 3.51 (s, 3H, C-12 OCH_3), 3.50 (m, 1H, C-16 OCH_2), 3.0 (s, 1H, C-9 H), 2.54 (m, 1H, C-14 H), 2.4-2.15 (m, 3H, C-15, C-6 H, C-4 H), 2.13 (s, 3H, C-1 COCH_3), 1.79 (s, 3H, C-13 H), 1.32 (s, 3H, C-10 CH_3), 1.25 (m, 3H, C-16 CH_3), 1.02 (s, 3H, C-8 CH_3), 1.01 (d, 3H, J =6.1 Hz, C-4 CH_3). IR: ν_{max} =1750, 1725, 1690, 1650 cm^{-1} .

1 β -acetyloxy-3-bromo-16-ethoxy-12-methoxypicras-12-ene-2,11-dione (14): To a cooled (-5°C) solution of **13** (34 mg, 0.076 mmol) in dry THF (5 ml) phenyl-trimethylammonium tribromide (PTAT, 30 mg, 0.0798) was added and the mixture was stirred for 1.5 h at this temperature. White crystals of phenyl trimethylammonium bromide precipitated at the bottom of the flask from the orange solution. The reaction mixture was poured into a mixture

of 0.1N $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ and saturated aqueous NaHCO_3 (10 ml 1:1) and extracted with ether (3x10 ml). The organic phase was washed with water (3x15 ml), brine (10 ml), dried (Na_2SO_4) and concentrated. Column chromatography of the residue (ethyl acetate-hexane3:1) yielded 17 mg (42%) of **14**. MS (EI) m/z (%)=528 [$\text{M}+\text{H}$]⁺ (23), 484 (42), 440 (100), 404 (35), 388 (17), 361 (67), 347 (17), 331 (13), 313 (7), 279 (9), 361 (67), 345 (17), 331 (13), 313 (7), 279 (9), 219 (8), 179 (18), 107 (4). ¹H NMR: δ =5.90 (s, 1H, C-3 H), 5.0 (m, 1H, C-1 H), 4.4 (m, 1H, C-16), 3.7 (m, 1H, C-7 H), 3.56 (m, 2H, C-16 OCH_2), 3.55 (s, 3H, C-12 OCH_3), 3.1 (s, 1H, C-9 H), 2.55 (m, 1H, C-14 H), 2.2-1.5 (m, 6H, C-15 H_2 , C-6 Hs, C-5 H), 2.15 (s, 3H, C-1 COCH_3), 1.8 (s, 3H, C-13 CH_3), 1.35 (s, 3H, C-10 CH_3), 1.1 (m, 3H, C-16 CH_3), 1.10 (d, 3H, J =6.1 Hz, C-4 CH_3), 1.05(s,3H,C-8 CH_3).

1 β -acetyloxy-16-ethoxy-12-methoxypicrasa-3,12-diene-2,11-dione (15): To a solution of **14** (12 mg,0.0227 mmol) in anhydrous DMF (5 ml), LiCO_3 (43 mg, 0.581mmol) and LiBr (42 mg,0.484mmol) were added and the mixture refluxed at 115°C for 2 h. The mixture was cooled, poured into water (10 ml), extracted with ether (3x10 ml), washed with brine (10 ml), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (ethylacetate:hexane3:1) to afford 5.3 mg (52%) of **15**. MS (EI) m/z (%)=447 [$\text{M}+\text{H}$]⁺ (24), 406 (100), 392 (17), 378 (6), 360 (7), 325 (5), 257 (3), 217 (4), 183 (13).High resolution MS calculated for $\text{C}_{25}\text{H}_{34}\text{O}_7$ (446.2305), Found= 446.2301. ¹H NMR (B): δ =6.04 (m, 1H, C-3 H), 5.26 (s, 1H, C-1 H), 5.0 (m, 1H, C-16 H), 3.76 (m, 1H, C-7H), 3.75-3.54 (m, 2H, C-16 OCH_2), 3.52 (s, 3H, C-12 OCH_3), 3.23 (m, 1H, C-5 H), 3.14 (s, 1H, C-9 H), 2.15 (s, 3H, C-1 COCH_3), 2.3-1.80 (m, 5H, C-15Hs, C-14 H, C-6Hs), 1.96 (s, 3H, C-4 CH_3), 1.81 (s, 3H, C-13 CH_3), 1.36 (s, 3H, C-10 CH_3), 1.25 (m, 3H, C-16 CH_3).

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