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SYNTHETIC STUDY TOWARDS THE TETRACYCLIC QUASSINOID SKELETON

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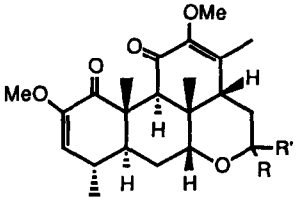
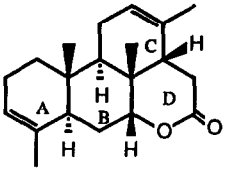
Abstract—The optically active tetracycle (**6**) with two *trans*-fused angular methyl groups is constructed from tiglic aldehyde and (*S*)-carvone in 9 steps involving a stereocontrolled aldol reaction and an *endo*-selective intramolecular Diels-Alder (IMDA) reaction.

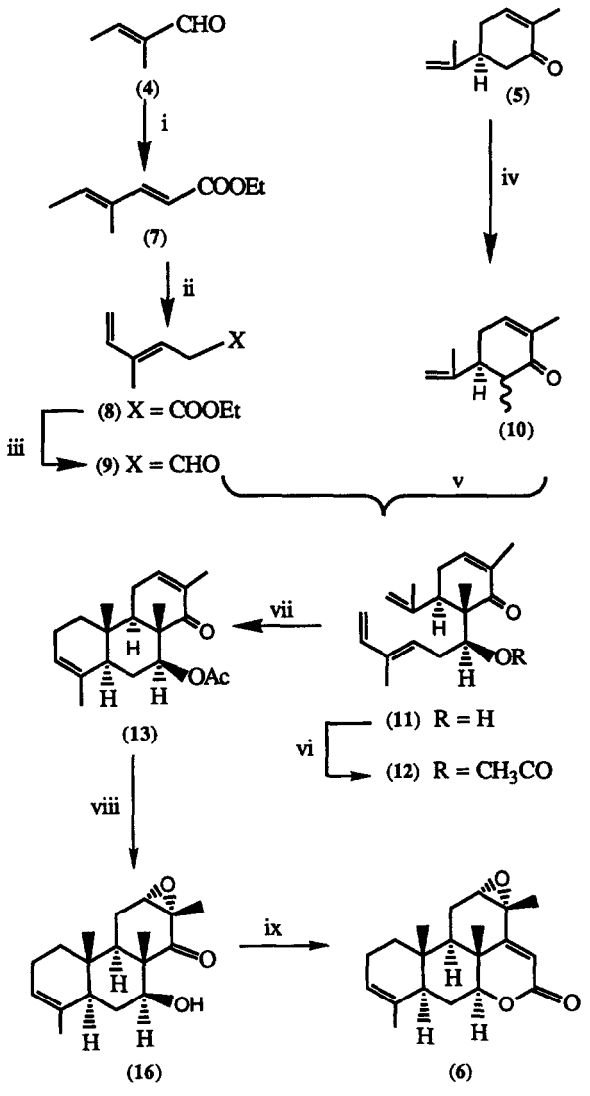
Since Valenta and his co-workers established the structure of quassin (**1**) and of neoquassin (**2**) in the early 1960's,[1] over 120 new triterpenoid bitter principles have been isolated from the *Simaroubaceae* plant family. These chemically related bitter constituents are named as quassinoids which have displayed a wide spectrum of biological activities[1,2] and present a significant synthetic challenge. Recently, the total syntheses of (±)-quassin (**1**),[3] (±)-catelanolide,[4] (±)-klaineanone,[5] and (±)-amarolide[6] have been reported. All these quassinoids share a basic tetracyclic carbon skeleton (**3**) with common stereochemical features. Substantial differences in the substitution pattern and oxidation level are found in the *A* and the *C* ring.[1] Our synthetic plan for the construction of (**3**) was based on the $C \rightarrow ABC \rightarrow ABCD$ ring formation strategy. We now describe, starting from commercially available tiglic aldehyde (**4**) and (*S*)-carvone (**5**), a rapid access to the optically active tetracycle (**6**), in which the two *trans*-fused angular methyl groups are fabricated *via* a stereocontrolled aldol reaction and an *endo*-selective intramolecular Diels-Alder (IMDA) reaction. A preliminary account on part of this work has appeared.[7]



(**1**) R,R' = O
(**2**) R' = OH, R = H



(**3**)



Scheme 1. *Reagents and conditions*: i, potassium t-butoxide, triethyl phosphonoacetate, THF, 20°C, (90%); ii, lithium di-isopropylamide (LDA), THF, then 10% aq. AcOH, -78°C, (85%); iii, DIBAL-H, toluene, -100°C; iv, LDA, MeI, THF, -10°C, (88%); v, LDA, then followed by aldehyde (9), THF, -100°C, (60%); vi, Et_3N, *N,N*-dimethylaminopyridine (DMAP), Ac_2O, CH_2Cl_2, (100%); vii, toluene, Methylene Blue, 220°C, 110 h, sealed tube, (80%); viii, t-butylhydroperoxide, triton B, methanol, then KOH, methanol, r.t., (85%); ix, NaH, triethyl phosphonoacetate, DME, reflux, (13%).

The short and enantioselective synthesis of the tetracycle (6) is illustrated in Scheme 1. Tiglic aldehyde (4) was olefinated with the potassium salt of triethyl phosphonoacetate in tetrahydrofuran (THF) into ethyl *E*,*E*-dienoate (7) which was deconjugated readily into the diene (8) in an overall yield of 77%.[3] The corresponding β,γ-unsaturated aldehyde (9), which underwent a facile conjugative isomerisation on isolation, was best prepared by partially reduction of the ester (8) with di-isobutylaluminium hydride (DIBAL-H) at -100 °C and used *in situ*. A stereocontrolled aldol reaction proceeded smoothly between the aldehyde (9) and the kinetic *E*-enolate derived from methyl carvone (10) {prepared from methylation[8] of (*S*)-carvone (5) under standard conditions}. The resultant *anti*-aldol (11) with two new chiral centres was isolated as a single diastereoisomer in an overall yield of 60% from (8) and (10). Presumably, the approach of the β,γ-unsaturated aldehyde (9) to the less hindered α-face of the *E*-enolate secured the desired stereochemistry of the angular methyl moiety and the stereochemical outcome of the hydroxyl group in (11) was then as expected from a six-centre chair-type transition state (see Fig. 1). This stereochemical result is consistent with the correlation[9] that *E*-enolates generally react with achiral aldehydes to give *anti*-aldols.

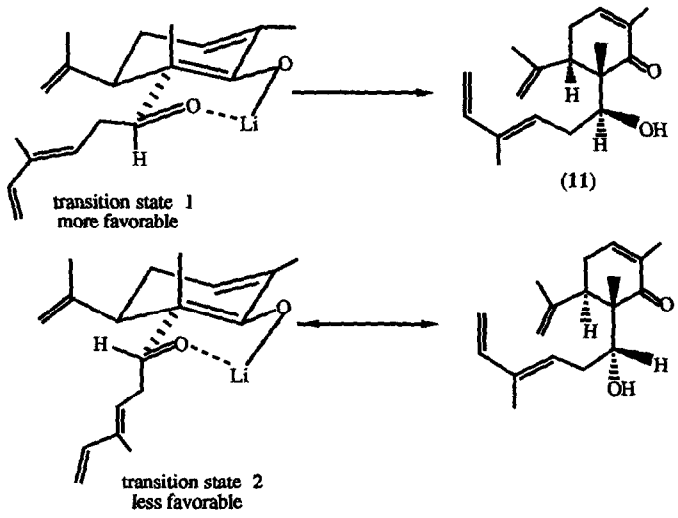
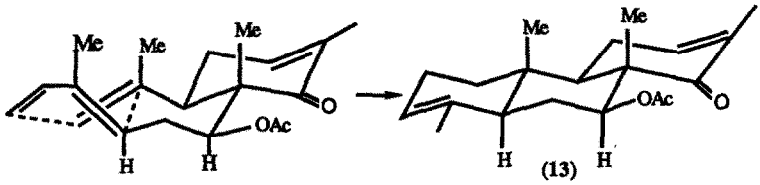


Fig. 1

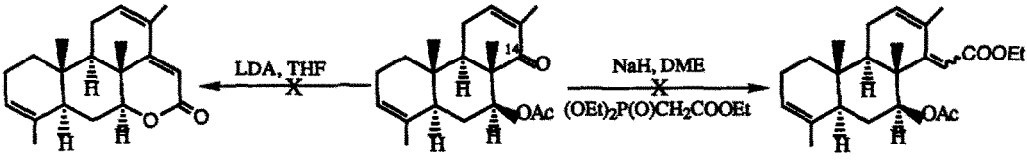
The IMDA precursor (11) containing a free hydroxy function underwent a retro-aldol reaction upon thermolysis and was therefore protected as the acetate (12). IMDA reaction[10] of (12) in a sealed tube then afforded cleanly the tricyclic ketone (13) as the sole product in 80% yield. The stereochemistry of the newly formed ring junction was established by an *X*-ray study[7] which demonstrated the IMDA reaction proceeded *via* the energetically most favourable chair-like transition state and was *endo*-selective (see Fig. 2).



endo-chair transition state

Fig. 2

After the construction of the *ABC* ring system, the formation of the lactone *D* ring was investigated. Thus the Wadsworth-Emmons-Horner[11] reaction was attempted to introduce an acetate unit onto the ketone (13). However, reaction of the enone (13) with the potassium salt of triethyl phosphonoacetate in THF or in 1,2-dimethoxyethane (DME) at room temperature or at reflux failed to furnish the dienoate (14) and only starting compound was recovered from the reaction mixture (Scheme 2). It was envisaged that keto-acetate (13) could be transformed into the lactone (15) *via* an intramolecular aldol condensation. However, treatment of (13) with lithium di-isopropylamide (LDA) in THF at various temperatures gave only starting material. The failure of the reactions may be attributable to the weak electrophilic ketone and to the steric congestion around C-14.



(15) (13) (14)

Scheme 2

In order to enhance the electrophilicity of the keto group, enone (13) was epoxidised with *tert*-butylhydroperoxide-triton B followed by alkaline hydrolysis to provide the hydroxy-epoxide (16) in 85% overall yield. The oxirane moiety in (16) should have the α-orientation, resulting from the attack of the epoxidising agent to the less hindered side of the enone. Finally, alkenation of (16) with the sodium salt of triethyl phosphonoacetate in DME under forcing conditions afforded the tetracycle (6) which has the *ABCD* ring system, but in only 13% yield.

Work is now in progress to improve the low yielding lactone formation and to transform the tetracycle (6) into optically active quassinoids and analogues.

Experimental

M.p.s were recorded on a Kofler block. ^{1}H N.m.r. spectra were recorded on a Varian SC300 spectrometer at 300 MHz using deuteriochloroform as solvent unless otherwise stated. Infra red spectra were recorded on a Perkin-Elmer 1710 Fourier Transform Spectrophotometer. Mass spectra were recorded on a Kratos MS25 instrument. Optical rotations were measured on an AA-100 polarimeter using ethanol as solvent unless otherwise stated. T.l.c. was performed on glass plates precoated with Merck silica $60F_{254}$. and compounds were visualised with a spray of 5% w/v dodeca-molybdophosphoric acid in ethanol and subsequent heating. THF and DME were distilled from sodium and benzophenone under dry nitrogen.

Ethyl (E,E)-*4-Methyl-2,4-hexadienoate* (**7**).

To a suspension of potassium *tert*-butoxide (8 g, 71.35 mmol) in dry THF (150 ml) under nitrogen was added dropwise triethyl phosphonoacetate (17.35 g, 77.25 mmol) at 20°C. After the mixture was stirred for 1 h at 20°C, *trans*-2-methyl-2-butenal (5 g, 59.45 mmol) (**4**) was added dropwise during 20 min. The mixture was stirred for further 2 h, quenched with water (20 ml), extracted with Et_2O (3 X 20 ml). The combined extracts were washed with cold brine, dried ($MgSO_4$), and concentrated to give an oily residue. Purification by distillation afforded the *ester* (**7**) (8.82 g, 90%) as a colourless oil, b.p. 110—112°C (5mm Hg), [lit.,[3] 95°C (1.1 mm Hg)]; R_F 0.60 [hexane-diethyl ether (9:1 v/v)]; $\nu_{max.}$ 1713 cm^{-1} (conjugated ester C=O); δ 1.20 (3 H, t, *J* 7.5 Hz), 1.67 (3 H, s), 1.72 (3 H, d, *J* 7.0 Hz), 4.09 (2 H, q, *J* 7.5 Hz), 5.67 (1 H, d, *J* 15 Hz), 5.88 (1 H, q, *J* 7.0 Hz), 7.22 (1 H, d, *J* 15 Hz); *m/z* (EI) 154 (58.4%, M^+), (CI) 155 (100%, MH^+).

Ethyl (E)-*4-Methyl-3,5-hexadienoate* (**8**).

To a solution of di-isopropylamine (8.8 ml, 66.24 mmol) in dry THF (160 ml) under nitrogen was added 1.6 M solution of n-butyllithium in hexane (37.28 ml, 57.11 mmol) followed by the dropwise addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10.96 ml, 90.86 mmol) at -78°C. After 10 min, the ester (**8**) (8 g, 51.92 mmol) was added dropwise. The mixture was kept with stirring for 4 h at -78°C, quenched with aqueous acetic acid (10% v/v; 80 ml). The solvent was evaporated and the residue was extracted with Et_2O (3 X 40 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to give an oily residue. Purification by distillation afforded the deconjugated *ester* (**8**) (6.8 g, 85%) as a colourless oil, b.p.97—99°C (10 mm Hg)[lit.,[3] 63°C (6.5 mm Hg)]; R_F 0.60 [hexane-diethyl ether (9:1 v/v)]; $\nu_{max.}$ 1738 cm^{-1} (saturated ester C=O); δ 1.25 (3 H, t, *J* 7.5 Hz), 1.72 (3 H, s), 3.17 (2 H, d, *J* 7.0 Hz), 4.13 (2 H, q, *J* 7.5 Hz), 5.05 (1 H, d, *J* 11 Hz), 5.15 (1 H, d, *J* 18 Hz), 5.68 (1 H, t, *J* 7.0 Hz), 6.40 (1 H, dd, *J* 18 and 11 Hz); *m/z* (EI) 154 (24.8%, M^+), (CI) 155 (100%, MH^+).

(S)-*6*-(α,β)-*Methylcarvone* (**10**).

To a solution of di-isopropylamine (7.44 ml, 54.22 mmol) in dry THF (60 ml) under nitrogen was added 1.6 M solution of n-butyllithium in hexane (30.12 ml, 51.24 mmol) at -10°C. The mixture was stirred for 5 min at -10°C and (*S*)-carvone (**5**) (6 g, 40.02 mmol) was then added dropwise. After 2 h at -10°C, iodomethane (34 ml, 0.54 mol) was added quickly and the mixture was then stirred for 0.5 h, quenched with H_2O (20 ml), concentrated and extracted with Et_2O (3 X 20 ml). The combined extracts were washed with cold brine, dried ($MgSO_4$) and concentrated *in vacuo* to give an oily residue. Purification by distillation afforded the *title compound* (**11**) (5.20 g, 88%) as a colourless oil, b.p. 165—167°C (15 mm Hg) [lit.,[8b] 135—170°C (35 mm Hg)]; R_F 0.65 [hexane-ether (9:1 v/v)]; $\nu_{max.}$ 1672 cm^{-1} (conjugated ketone C=O); δ 1.05 (3 H, d, *J* 6.5 Hz), 1.06 (3 H, d, *J* 6.5 Hz), 1.70 (3 H, s), 1.76 (3 H, s), 2.15-2.60 (4 H, m), 4.80 (2 H, bs), 6.69 (1 H, bs); *m/z* (EI) 165 (17.2%, MH^+).

(E)-*4-Methyl-3,5-hexadienal* (**9**).

To a solution of the ester (**8**) (0.5 g, 3.25 mmol) in dry toluene (5 ml) under nitrogen was added 1.5 M solution of DIBAL-H in toluene (5.41 ml, 8.11 mmol) during 20 min at -100°C. After the addition was completed, the solution was kept with stirring for 1 h at -100°C, and quenched with glacial acetic acid (0.46 ml, 8.11 mmol). The desired *aldehyde* (**9**) was formed. The mixture was maintained at -100°C and was used directly in the next reaction.

Triene-alcohol (**11**).

To a solution of di-isopropylamine (0.57 ml, 4.05 mmol) in dry THF (7 ml) under nitrogen was added dropwise 1.6 M solution of n-butyllithium in hexane (2.44 ml, 3.90 mmol) at -78°C. After the mixture was stirred for 10 min at -78°C, the methyl carvone (**10**) (0.53 g, 3.25 mmol) in THF (4 ml) containing 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (0.65 ml, 5.33 mmol) was added dropwise. The mixture was stirred for 1 h and cooled to -100°C. The reaction mixture of the aldehyde (**10**) prepared in the previous experiment was added in one portion. The mixture was kept with stirring for 5 min at -100°C under nitrogen, and quenched with saturated aqueous NH_4Cl (10 ml). Solvent removal gave a residue which was extracted with Et_2O (3 X 20 ml). The combined extracts were washed with brine (10 ml), dried ($MgSO_4$), and concentrated *in vacuo* to afford an oily residue. Purification by flash chromatography on silica gel [hexane-diethyl ether (3:1 v/v)] afforded the *alcohol* (**11**) (0.5 g, 60%) as a colourless oil, $[\alpha]_D$ -4.4° (*c* 1.9); R_F 0.30 [hexane-diethyl ether (3:1 v/v)]; $\nu_{max.}$ 3479 (OH) and 1663 cm^{-1} (conjugated ketone); δ 1.08 (3 H, s), 1.65 (1 H, s), 1.69 (3 H, s), 1.78 (6 H, s), 2.3-2.7 (4 H, m), 2.98 (1 H, t, *J* 6 Hz), 3.86 (1 H, dd, *J* 10.5 and 2.5 Hz), 4.80 (1 H, s), 4.85 (1 H, s), 4.96 (1 H, d, *J* 10.5 Hz), 5.12 (1 H, d, *J* 17.5 Hz), 5.62 (1 H, t, *J* 7 Hz), 6.38 (1 H, dd, *J* 17.5 and 10.5 Hz,), 6.59 (1 H, bs); *m/z* (CI, NH_3) 275 (14.1%, MH^+) (Found: C, 78.7; H, 9.6. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.5%).

Triene-ester (**12**).

To a stirred solution of alcohol (**11**) (30 mg, 0.11 mmol), triethylamine (66.38 mg, 0.66 mmol) and DMAP (2.68 mg, 0.022 mmol) in dry CH_2Cl_2 (1 ml) was added dropwise acetic anhydride (55.84 mg, 0.55 mmol) under nitrogen at room temperature. The mixture was stirred at room temperature for 18 h and concentrated *in vacuo*. Purification by flash chromatography on silica gel [hexane-diethyl ether (4:1 v/v)] afforded the *ester* (**12**) (34.6 mg, 100%) as a pale yellow oil, $[\alpha]_D$ +17.1° (*c* 1.3); R_F 0.45 [hexane-diethyl ether (3:1 v/v)]; $\nu_{max.}$ 1743 (ester C=O) and 1673 cm^{-1} (conjugated ketone C=O); δ 1.08 (3 H, s), 1.59 (3 H, s), 1.72 (3 H, s), 1.78 (3 H, s), 1.92 (3 H, s), 2.2-2.9 (5 H, complex m), 4.70 (1 H, s), 4.76 (1 H, s), 4.96 (1 H, d, *J* 10.5 Hz), 5.12 (1 H, d, *J* 17.5 Hz), 5.35-5.50 (2 H, complex m), 6.32 (1 H, dd, *J* 17.5 and 10.5 Hz), 6.55 (1 H, bs); *m/z* (CI, NH_3) 334 (9.8%, MNH_4^+) (Found: C, 75.6; H, 8.7. $C_{20}H_{28}O_3$ requires C, 76.0; H, 8.9%).

Tricyclic-keto-ester (**13**).

A pyrex tube was charged with a solution of triene ester (**12**) (0.1 g) and methylene blue (2 mg) in dry toluene (50 ml). The tube was sealed *in vacuo* and maintained at 220°C for 110 h. After the reaction mixture was cooled to room temperature, the sealed tube was opened and the contents were concentrated *in vacuo*. Purification by flash chromatography on silica gel [hexane-diethyl ether (3:1 v/v)] afforded the *tricycle* (**13**) (0.08 g, 80%, based on the recovery of starting compound) as a white solid, m.p. 138—140°C; $[\alpha]_D$ +89.8° (*c* 0.61); R_F 0.35 [hexane-diethyl ether (3:1 v/v)]; $\nu_{max.}$ 1736 (ester C=O) and 1678 cm^{-1} (ketone C=O); δ (C_6D_6) 0.78 (3 H, s), 1.21 (3 H, s), 1.59 (3 H, s), 1.82 (3 H, s), 1.2-2.0 (9 H, complex m), 2.01 (3 H, s), 2.28 (1 H, ddd, *J* 12, 5 and 2 Hz), 5.29 (1 H, bs), 5.50 (1 H, dd, *J* 12 and 5 Hz), 6.04 (1 H, bs); *m/z* (EI) 317 (100%, MH^+) (Found: C, 76.1; H, 8.9. $C_{20}H_{28}O_3$ requires C, 76.0; H, 8.9%).

Epoxy-alcohol (**16**).

To a solution of the enone (**13**) (0.5 g, 1.58 mmol) in THF (15 ml) was added a solution of triton B (40%, 1.58 ml) in methanol followed by an aqueous solution of *tert*-butylhydroperoxide (70%, 1.58 ml) at room temperature. The mixture was stirred for 20 h and the solvent was removed *in vacuo*. The residue was extracted with diethyl ether (3 X 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. A solution of potassium hydroxide (0.5 g) in methanol (5 ml) was added to the residue. The reaction mixture was stirred for 24 h at room temperature and concentrated. The residue was acidified with aqueous hydrochloric acid (10% v/v, 5 ml) and extracted with diethyl ether (3 X 10 ml). The combined extracts were washed with brine (5 ml), dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel [hexane-diethyl ether (4:1 v/v)] afforded the *epoxy-alcohol* (**16**) (0.47 g, 85%) as a white solid, m.p. 110—112°C; $[\alpha]_D$ +4.2° (*c* 1.0, CH_2Cl_2); R_F 0.48 [hexane-diethyl ether (4:1 v/v)]; $\nu_{max.}$ 3544 (OH) and 1696 cm^{-1} (deconjugated C=O); δ 0.82 (3 H, s), 1.13 (3 H, s), 1.40 (3 H, s), 1.61 (3 H, s), 2.2-1.2 (10 H, m), 2.36 (1 H, ddd, *J* 12, 5, and 2 Hz), 3.38 (1 H,

bs), 3.95 (1 H, dd, *J* 12 and 5 Hz), 5.30 (1 H, bs); *m/z* (EI) 290 (53.2%, M^+) (Found: C, 74.7; H, 9.2. $C_{18}H_{26}O_3$ requires C, 74.5; H, 9.0%).

Tetracyclic-lactone (**6**).

Sodium hydride (80% in oil; 41.76 mg, 1.74 mmol) was washed with dry pentane (2 X) under nitrogen, suspended in DME (4 ml) and the mixture was cooled to O°C. Triethyl phosphonoacetate (244.4 mg, 1.09 mmol) was added dropwise to the stirred suspension. After 1 h, a solution of the keto-alcohol (**16**) (70 mg, 0.243 mmol) in DME (1 ml) was added dropwise and the mixture was heated under reflux overnight. The resulting mixture was diluted with water (5 ml) and extracted with dichloromethane (3 X 10 ml). The combined extracts were washed with water (5 ml), dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel [hexane-diethyl ether (1:1 v/v)] afforded the lactone (**6**) (10 mg, 13%) as a white solid, m.p. 168—170°C; $[\alpha]_D$ +46.7° (*c* 0.3, CH_2Cl_2); R_F 0.45 [hexane-diethyl ether (1:1 v/v)]; $\nu_{max.}$ 1719 cm^{-1} (conjugated ester C=O); δ 0.86 (3 H, s), 1.18 (3 H, s), 1.53 (3 H, s), 1.66 (3 H, s), 2.2-1.2 (9 H, m), 2.18 (1 H, ddd, *J* 12, 4 and 2 Hz), 3.35 (1 H, bs), 4.13 (1 H, dd, *J* 12 and 4 Hz), 5.33 (1 H, bs), 6.12 (1 H, bs); *m/z* (EI) 315 (100%, MH^+) (Found: C, 76.5; H, 7.8. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%).

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