Synthesis of Optically Active Tetracyclic Quassinoid Skeleton

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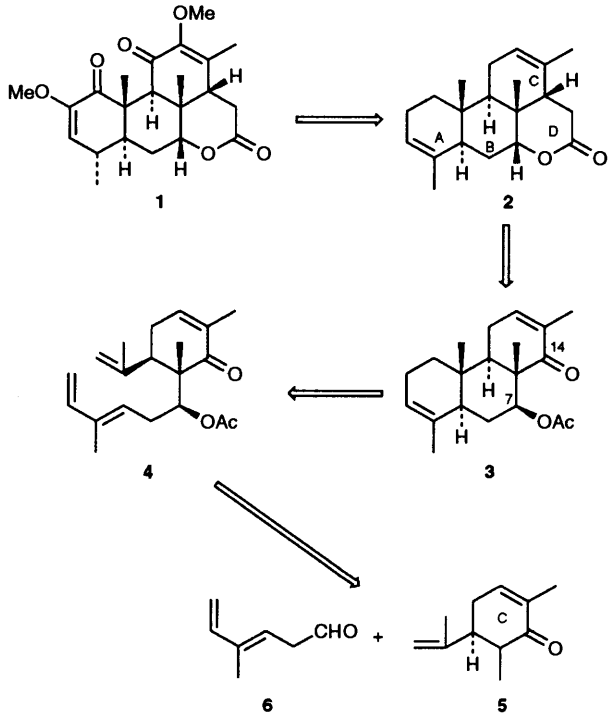
Tetracyclic quassinoid skeletons **2** and **22** with six correct chiral centres common to numerous quassinoids are constructed from (*S*)-carvone and 3-methylsulfolene by a 16-step and 13-step reaction sequence involving highly regioselective and stereocontrolled reactions.

The quassinoids constitute a large and constantly expanding group of terpenoid bitter principles found in the *Simaroubaceae*, a large plant family of pantropical distribution.[1] The highly oxygenated carbon frameworks containing many contiguous chiral centres and the wide spectrum of biological properties[1,2] of the quassinoids have engendered massive synthetic efforts[3] from many research groups. Fruitful results in quassinoid synthesis produced ingenious total syntheses of five tetracyclic and two pentacyclic members of the C_{20} picrasane family in racemic forms by groups led by Grieco,[4] Takahashi,[5] Murae,[6] and Valenta.[7] More recent and equally impressive works from the Grieco group have furnished the syntheses of bruceantin,[8] simalikalactone D,[9] and quassimarin.[10] Interest in enantioselective routes to quassinoids began with early investigations by Dias,[11] Graf,[12] Ziegler,[13] Fukumoto[14] and Schlessinger[15] and resulted in the first total syntheses of (+)-picrasin B, (+)-Δ^2-picrasin B and (+)-quassin by Watt's group[16] using the (−)-enantiomer of the Wieland–Miescher ketone as the starting material. Although the biological activity resided mainly in the pentacyclic series, prudent assembly of the tetracyclic member would be a suitable vehicle for testing the methodology needed for the construction of the pentacyclic quassinoids.

In developing an enantiospecific synthesis of a tetracyclic quassinoid such as (+)-quassin **1**, we were interesting in the construction of the quassinoid skeleton **2** which has the general ABCD ring system with six chiral centres common to numerous quassinoids.[1] We recently reported on the convergent synthesis of the ABC ring system[17] of structure **2**. We now describe an improvement of our previous effort and the successful synthesis of compounds **2**[18] and **22** in detail.

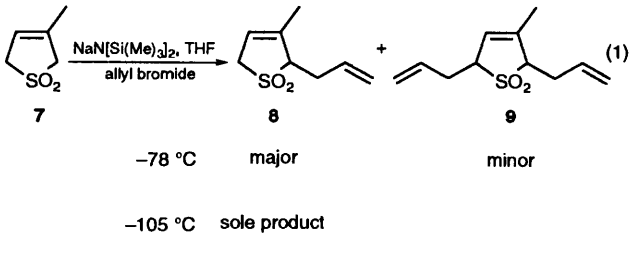


Scheme 1 Retrosynthetic scheme to (+)-quassin **1**

Results and Discussion

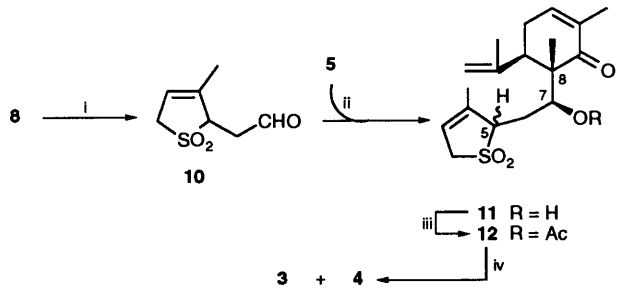
Our synthetic strategy for the fabrication of **2** is based on the C ⟶ ABC ⟶ ABCD ring annulation sequence as shown in Scheme 1. The skeleton **2** might be derived from the tricyclic keto ester **3** which might in turn be constructed by an *endo*-selective intramolecular Diels–Alder (IMDA) reaction of the triene **4**. The triene **4** in turn might be obtained *via* a stereoselective aldol reaction between the enolised methylcarvone **5** and (*E*)-4-methyl-3,5-hexadienal **6** which might itself be prepared from the commercially available 'tiglic aldehyde'. [(*E*)-2-methylbut-2-enal].

The first problem in our previous work was the synthesis of the unstable and volatile diene aldehyde **6**.[17] In our hands, compound **6** was best prepared by partial reduction of its corresponding ethyl ester with diisobutylaluminium hydride (DIBAH) at −100 °C and used directly in the subsequent aldolisation.[17] However, good yields of the aldol product were sporadic and this led us to explore an alternative avenue. Recently, the device of using substituted 2,5-dihydrothiophene *S*,*S*-dioxides (sulfolenes) as precursors of conjugated dienes has drawn increasing attention.[19] It has been found that attachment of an alkyl group to 3-methylsulfolene **7** could be achieved regioselectively at C-2 and the cheletropic extrusion of SO_2 would then produce the corresponding conjugated diene with the C-2,3 double bond exclusively *E*.[19,20] In line with this strategy, we envisaged that masking of the diene moiety in substrate **6** as a sulfolene derivative would afford a relatively stable aldehyde **10** amenable to high yielding aldolisations. Thus, deprotonation of compound **7** with $NaN[Si(Me)_3]_2$ in tetrahydrofuran (THF) at −78 °C followed by the addition of an excess amount of allyl bromide afforded a mixture of monoalkylated product **8** and dialkylated compound **9**. Lowering of the reaction temperature to −105 °C gave the desired alkene **8** in 96% yield as the sole product [eqn (1)]. The regioselectivity of



this reaction was attributable to the formation of the more substituted (although more hindered) allylic carbanion.[20] However, we reason that the electron-donating effect of the methyl group in compound **7** induces a higher electron density around C-4, thus rendering the protons at C-5 comparatively less acidic than those at C-2.

Selective hydroxylation of the terminal double bond in compound **8** with a catalytic amount of OsO_4 and 1 mole equivalent of 4-methylmorpholine *N*-oxide (MNO) followed by glycol cleavage oxidation of the resulting diol with 3 mole equivalents of sodium metaperiodate furnished the protected diene aldehyde **10** in 60% overall yield as a yellow oil (Scheme 2). The aldehyde **10** was stable in a freezer (−10 °C) for several

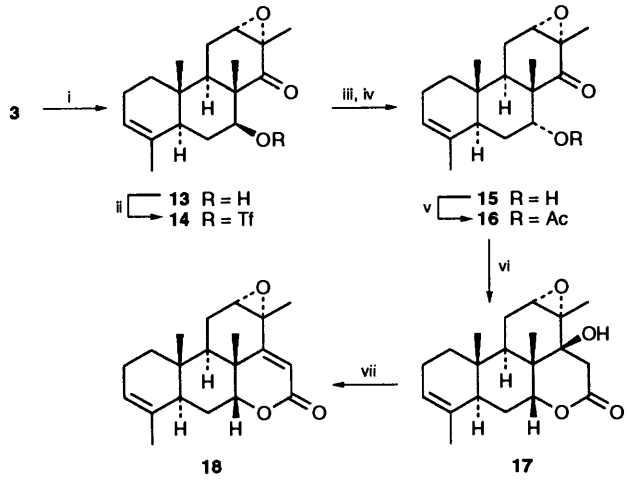


Scheme 2 *Reagents and conditions:* i, OsO_4, MNO, aq. 1,4-dioxane; then $NaIO_4$, aq. MeOH (60%); ii, LDA, followed by aldehyde **10**, THF, DMPU, −78 °C (87%); iii, Ac_2O, pyridine, DMAP, CH_2Cl_2, room temp. (89%); iv, PhCN, Methylene Blue, 190 °C, 110 h (62%)

weeks. With compound **10** in hand, we went on to investigate its aldolisation. Formation of the kinetic enolate of methylcarvone **5** [prepared by methylation of (+)-carvone][21] with lithium diisopropylamide (LDA) in THF/1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) at −78 °C followed by the addition of the aldehyde **10** gave the aldol **11** in 87% yield as a mixture of two diastereoisomers (~1 : 1, epimeric at C-5) which did not need to be separated. Although we did not have evidence to confirm the stereochemistry of the two newly formed chiral centres at C-7 and C-8, we believed that the aldol reaction should give us the *anti*-product[22] with a β-hydroxy group at C-7 and a β-methyl group at C-8 based on previous observations.[17] Acetylation of the alcohol **11** with Ac_2O in the presence of pyridine and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 gave the IMDA precursor **12** in 89% yield.

In our previous work,[17] the sealed-tube technique was used successfully to carry out the IMDA[23] reaction. In this work, we reckoned that the extrusion of SO_2 at high temperature might cause trouble in a sealed system and decided to attempt other methods. In our hands, the IMDA reaction was achieved by a simple one-pot operation. Boiling of a dilute solution of the sulfolene **12** in benzonitrile[24] under nitrogen for 110 h provided the tricyclic keto ester **3** in 62% yield as a single diastereoisomer. A small amount of the known triene **4**[17] was also isolated from the reaction mixture. Both products **3** and **4** were identical with those reported previously.[17] It therefore appears that, under these conditions, the sulfolene **12** underwent a stereospecific SO_2 extrusion and an *endo*-selective IMDA reaction to furnish the *trans*-fused AB ring system **3**. The high reaction temperature and long reaction time led us to believe that the stereoselectivity of the IMDA reaction was simply thermodynamically controlled.

With an efficient and expeditious route to the optically active tricycle **3** available, we set out to tackle the second problem in our previous work,[17] *i.e.* the assembly of the D ring to complete the construction of the quassinoid skeleton **2**. Our previous work[17] has shown that the enolised C-7 acetate in compound **3** failed to undergo an intramolecular aldol-type reaction with the C-14 keto group because of steric hindrance. It appeared to us that inversion of the configuration at C-7 in compound **3** to the desired α-acetate might give us an opportunity to achieve the intramolecular aldol cyclisation. Thus, epoxidation of enone **3** followed by deacetylation as described previously[17] gave the known alcohol **13** (Scheme 3). Although attempts involving the

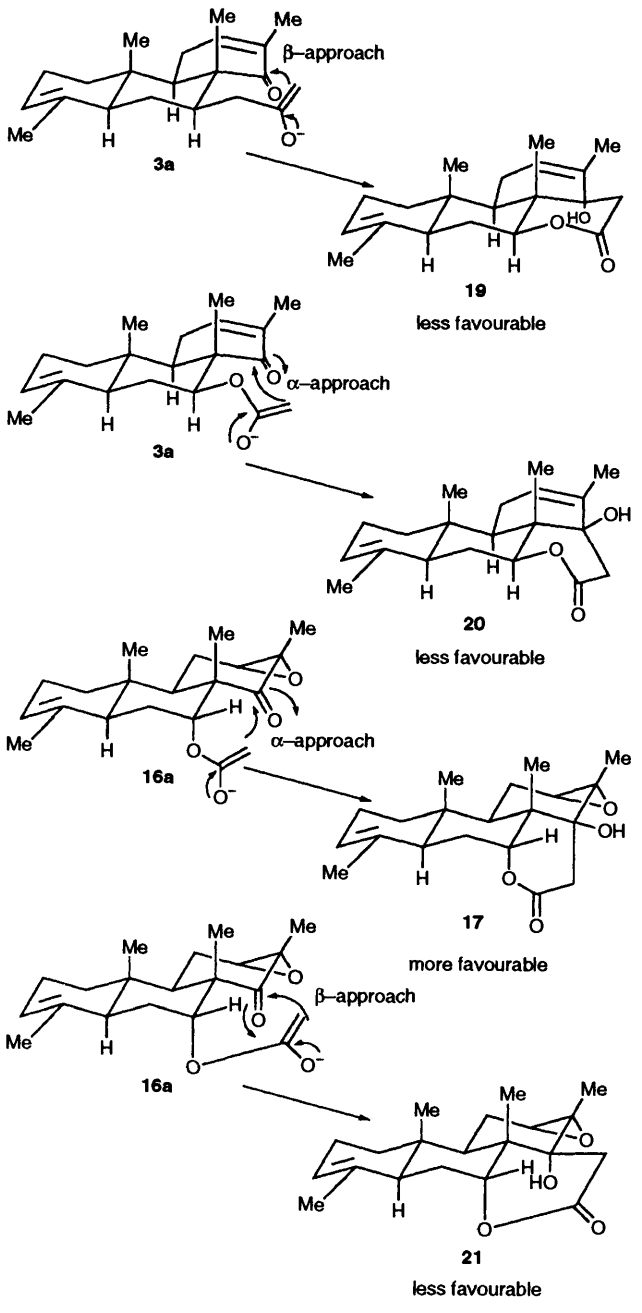


Scheme 3 *Reagents and conditions:* i, Bu^tO_2H, Triton B, MeOH; then KOH, MeOH (85%); ii, Tf_2O, pyridine, DMAP, CH_2Cl_2,0 °C; iii, wet DMF, room temp.; iv, K_2CO_3, MeOH, room temp. (60%); v, Ac_2O, pyridine, DMAP, CH_2Cl_2, room temp. (100%); vi, LDA, THF, DMPU, −78 to 0 °C (98%); vii, $SOCl_2$, pyridine, 0 °C (98%)

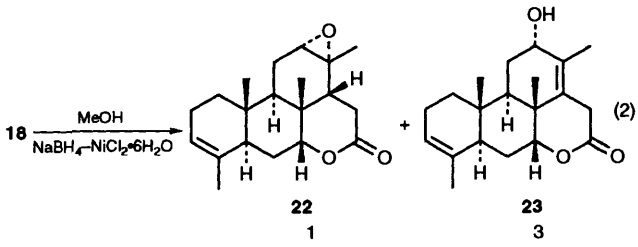
Mitsunobu reaction[25] were unproductive, the stereochemistry of the alcohol in compound **13** was successfully inverted, *via* a 3-step reaction sequence. Thus, esterification of the alcohol **13** with $(CF_3SO_2)_2O$ (Tf_2O) in the presence of pyridine and a catalytic amount of DMAP in CH_2Cl_2 gave the triflate **14**. Nucleophilic displacement of $CF_3SO_2^-$ from compound **14** with wet *N*,*N*-dimethylformamide (DMF) and subsequent hydrolysis of the formyl group thus formed with potassium carbonate in methanol led to the α-alcohol **15** in an overall yield of 60%. The ^1H NMR spectrum of the α-alcohol **15** showed that the 7-H appeared at δ 4.19 as a triplet ($J_{7,6\alpha} = J_{7,6\beta} = 3.9$ Hz); the small coupling constant is consistent with 7-H being in the equatorial position. In comparison, the ^1H NMR spectrum of compound **13** displayed the 7-H signal at δ_H 3.95 as a doublet of doublets ($J_{7,6\alpha}$ 4.2, $J_{7,6\beta}$ 11.5 Hz) and hence supported our assignment of the β-hydroxy group at C-7 in this case. Subsequent acetylation of compound **15** afforded the ester **16** in quantitative yield.

At this stage, the ester **16** was treated with LDA in THF–DMPU from −78 to 0 °C to induce an intramolecular aldol addition. Indeed, the lactone **17** was isolated in 98% yield as a single diastereoisomer. Modelling studies showed that the intramolecular aldol cyclisation of compound **3a** failed to give compound **19** partially because the axial methyl group at C-8 presented strong steric effect to block the β-face approach. The attack from the less hindered α-face was also an unfavourable process because the newly formed lactone D ring in compound **20** was in a twisted boat conformation. On the other hand, the cyclisation of compound **16a** would undergo a favourable α-axial attack to give the lactone **17** whereas the formation of compound **21** (boat conformation) was less favourable.

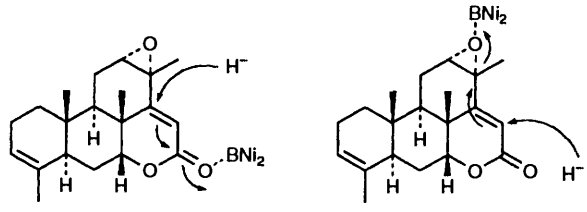
Dehydration of the β-hydroxy lactone **17** by using thionyl dichloride in pyridine at 0 °C proceeded smoothly to give the α,β-unsaturated lactone **18** in 98% yield. The driving force in this reaction should be the formation of the thermodynamically more stable conjugated system. A strong band located at 1720 cm^{-1} (conjugated lactone C=O) was observed in the IR spectrum of compound **18**, and the ^1H NMR spectrum showed that the olefinic proton 15-H at δ_H 6.15 was a singlet.



For the completion of the D ring, a regioselective and stereoselective reduction of the conjugated carbon–carbon double bond was required. After much experimentation, the selective reduction was achieved with the $NaBH_4$–$NiCl_2$·$6H_2O$ system.[26] When sodium boranuide (sodium borohydride) was added in small portions into a methanolic solution of compound **18** in the presence of a catalytic amount of $NiCl_2$·$6H_2O$ at −25 °C, a black precipitate appeared immediately. After being stirred at −25 °C for 1 hour, the reaction mixture afforded a 1:3 mixture of compounds **22** and **23**, respectively, in 70% yield [eqn (2)]. The mechanism is of $NaBH_4$–$NiCl_2$·$6H_2O$ reduction is not fully understood. Presumably, the black precipitate was Ni_2B which was generated by sodium boranuide reduction of $NiCl_2$.[26] Reaction of compound **18** with Ni_2B might form a kind of boron complex at the oxygen atom of the lactone carbonyl or of the oxirane which was subsequently reduced by the hydride (see structures **18a** and **18b**). The regioselectivity of this reduction might be rationalised in terms of the steric hindrance at C-14 and C-15 positions.

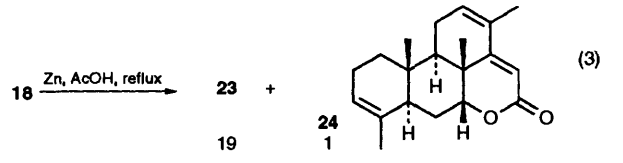


Hydride attack at C-14 (**18a**) would give the epoxy lactone **22** whereas reduction at C-15 (**18b**) would afford the allylic alcohol **23**. Since C-15 position is less substituted (less sterically hindered), compound **23** is the preponderant product. The stereoselectivity for the formation of compound **22** might be attributed to the more favourable attack of the hydride source from the 'free' β-face instead of the 'crowded' α-face.

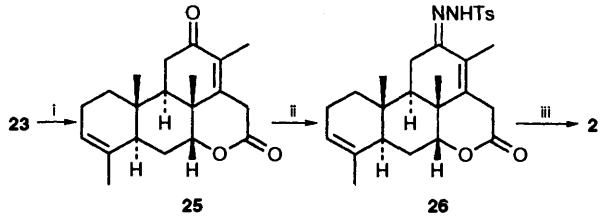


The structure of the tetracyclic quassinoid skeleton **22** was confirmed by nuclear Overhauser enhancement (NOE) experiments. The NOE effects between 7-H and 14-H indicated that these protons were located near each other, therefore these protons have the β-equatorial stereochemistry. The NOE effects between 7-H, 14-H, the methyl groups at C-8 and at C-10 supported this assignment. The stereochemistry of the oxirane functionality in the C ring was also confirmed as in the α-face by the NOE effects between 12-H, the methyl groups at C-13 and at C-8.

The allylic alcohol **23** could also be obtained in 57% yield by treatment of epoxide **18** with zinc powder in refluxing acetic acid. A very small amount of a by-product **24** was isolated from reaction mixture [eqn (3)]. Since attempts to increase the

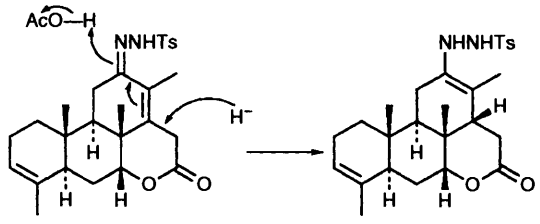


yield of compound **22** in the $NaBH_4$–$NiCl_2$ reduction failed to give satisfactory results, it was decided to transform the alcohol **23** into the target skeleton **2**. Thus, pyridinium chlorochromate (PCC) oxidation of allylic alcohol **23** in CH_2Cl_2 afforded the enone **25** in 91% yield (Scheme 4). A modified Wolf–Kishner



Scheme 4 *Reagents and conditions:* i, PCC, 3 Å molecular sieves, CH_2Cl_2, room temp. (91%); ii, $TsNHNH_2$, EtOH, reflux; iii, $NaBH_3CN$, AcOH, 70 °C (50%)

deoxygenation[27] was applied by treatment of enone **25** with tosylhydrazine to afford the tosylhydrazone derivative **26** which then underwent reductive rearrangement with sodium cyanoboranuide in acetic acid[28] at 70 °C to furnish the tetracyclic quassinoid skeleton **2** as a single diastereoisomer in 50% overall yield. A plausible mechanism involves an initial conjugate addition of hydride at C-14 from the less hindered β-face followed by double-bond migration, leading to the correct stereochemistry at C-14. Sequential loss of TsH and nitrogen from compound **27** would then yield the quassinoid skeleton **2**. The ^{1}H NMR spectrum of compound **2** showed that 14-H appeared at δ 1.89 as a doublet of doublets ($J_{14,15\beta}$ 6.9, $J_{14,15\alpha}$ 11.5 Hz) and was very similar to that of the 14-H which appeared in the ^{1}H NMR spectrum of compound **22** [δ 1.92 doublet of doublets ($J_{14,15\beta}$ 7, $J_{14,15\alpha}$ 12 Hz)].



26a **27**

In summary, the optically active skeletons **22** and **2** were synthesized from (+)-carvone and 3-methylsulfolene by a 13-step and 16-step reaction sequence, respectively.

Experimental

General.—M.p.s were recorded on a Kofler block, and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 Fourier transform spectrometer for thin films on NaCl plates or KBr discs, unless otherwise stated. 300 MHz ^{1}H NMR were recorded on a Bruker AC300E spectrometer or a Varian XL300 spectrometer using tetramethylsilane as internal standard. The solvent was $CDCl_3$, unless otherwise stated. *J*-Values are given in Hz. Mass spectra were recorded on a Kratos MS30 instrument coupled to a Kratos DS55 data system and accurate mass measurement (± 5 ppm) on a Kratos DS25 instrument, also coupled to a Kratos DS55 data system. For chemical ionisation, ammonia was the reagent gas, unless otherwise stated. Elemental analyses were determined by the Microanalysis Section of the Chemistry Department at Manchester University. TLC were carried out on plates precoated with Merck Silica $60F_{254}$. Visualisation was achieved by UV irradiation, exposure to iodine vapor or by immersion in either a 20% solution of dodecamolybdophosphoric acid in EtOH or a 20% cerium(IV) sulfate solution in dil. H_2SO_4, with subsequent heating. Optical rotations were measured on an AA-100 polarimeter using CH_2Cl_2 as solvent, unless stated otherwise. $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}. MeOH was dried by being refluxed over magnesium and then distilled from its magnesium salt under nitrogen. CH_2Cl_2 was dried by being refluxed over and distilled from CaH_2 under nitrogen. THF was dried by being refluxed over and distilled from sodium metal under nitrogen, with benzophenone as indicator. DMPU and DMF were dried over 4 Å molecular sieves. Pyridine and triethylamine were dried by distillation from KOH pellets under nitrogen. Diisopropylamine was dried by being refluxed over and distilled from CaH_2 under nitrogen. Where appropriate, reactions were performed under nitrogen or argon and, for all the reactions described, stirring was performed magnetically or mechanically. Light petroleum refers to the fraction with distillation range 40–60 °C.

3-Methyl-2-(prop-2-enyl)-2,5-dihydrothiophene 1,1-Dioxide **8**.—To a solution of 3-methyl-2,5-dihydrothiophene 1,1-dioxide **7** (2 g, 15.15 mmol) in dry THF (100 cm^3) was added dropwise a 1.0 mol dm^{-3} solution of $NaN[Si(Me)_3]_2$ (13.64 cm^3, 13.64 mmol) over a period of 40 min at −105 °C. The reaction mixture was stirred for 1 h and quenched with allyl bromide (3.88 cm^3, 45.45 mmol). The reaction mixture was stirred at −105 °C for 10 min and poured into saturated aq. NH_4Cl (50 cm^3). The aqueous phase was extracted with CH_2Cl_2 (4 × 20 cm^3), and the extracts were washed with brine (2 × 20 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification through flash column chromatography [hexane–EtOAc (4:1 v/v)] yielded the *title compound* **8** (2.5 g, 96%) as an oil, R_f 0.43 [hexane–EtOAc (4:1 v/v)]; δ_H 1.87 (3 H, s), 2.62 (2 H, m), 3.65 (3 H, m), 5.17 (1 H, dd, *J* 10 and 1.2), 5.23 (1 H, dq, *J* 17 and 1.2), 5.69 (1 H, br) and 5.88 (1 H, m); *m/z* (CI, NH_3) 190 (100%, MNH_4^+) (Found: $M^+ - SO_2$, 108.0942. C_8H_{12} requires M, 108.0939).

(3-Methyl-1,1-dioxo-2,5-dihydro-1λ^6-thiophen-2-yl)acetaldehyde **10**.—A solution of the alkene **8** (0.25 g, 1.45 mmol), MNO (0.17 g, 1.45 mmol), water (2 cm^3), 1,4-dioxane (6 cm^3) and a catalytic amount of OsO_4 was stirred at room temperature for 24 h. After the mixture had cooled, saturated aq. $Na_2S_2O_3$ (5 cm^3) was added and the reaction mixture was passed through a short column of silica gel, which was then washed with ethyl acetate (30 cm^3). The combined eluent was concentrated to give the corresponding diol as a yellow oil.

The diol was dissolved in a mixture of MeOH (5 cm^3) and water (2 cm^3), and $NaIO_4$ (0.35 g, 1.62 mmol) was added. The reaction mixture was stirred overnight at room temp. and poured into saturated aq. NH_4Cl (5 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined extracts were washed with brine (2 × 5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [hexane–EtOAc (2:1 v/v)] yielded the *aldehyde* **10** (0.15 g, 60%) as an oil, R_f 0.44 [hexane–EtOAc (1:1.5 v/v)]; ν_{max}/cm^{-1} 1722 (C=O); δ_H 1.80 (3 H, s), 2.85 (1 H, dd, *J* 19 and 5), 3.09 (1 H, dd, *J* 19 and 7.5), 3.73 (2 H, m), 4.11 (1 H, br), 5.62 (1 H, br) and 9.89 (1 H, s); *m/z* (EI) 174 (1.7%, M^+).

Keto Alcohol **11**.—To a solution of diisopropylamine (0.54 cm^3, 3.85 mmol) in dry THF (5 cm^3) under nitrogen was added 1.6 mol dm^{-3} butyllithium in hexane (2.41 cm^3, 3.85 mmol) at −78 °C. After the reaction mixture had been stirred for 10 min at −78 °C, a solution of the methylcarvone **5**[21] (0.5 g, 3.5 mmol) in THF (1.5 cm^3) containing DMPU (1 cm^3) was added dropwise. The reaction mixture was stirred for 1 h and the aldehyde **10** (0.67 g, 3.85 mmol) was added in one portion. The reaction mixture was stirred for 5 min at −78 °C under nitrogen, and quenched with saturated aq. NH_4Cl (5 cm^3). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 cm^3) and the combined extracts were washed with brine (2 × 2 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [light petroleum–diethyl ether (1:5 v/v)] yielded the *keto alcohol* **11** (0.9 g, 87%) as an oil (a 1:1 mixture of diastereoisomers), R_f 0.54 (Et_2O); ν_{max}/cm^{-1} 3495 (OH) and 1663 (enone C=O); δ_H(*inter alia*) 1.09 (1.5 H, s, 8-Me) and 1.19 (1.5 H, s, 8-Me); *m/z* (CI, NH_3) 356 (6.5%, MNH_4^+) (Found: C, 63.5; H, 8.1. $C_{18}N_{26}O_4S$ requires C, 63.9; H, 7.7%).

Keto Ester **12**.—To a solution of the alcohol **11** (0.64 g, 1.89 mmol), pyridine (0.91 cm^3, 11.34 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (10 cm^3) was added acetic anhydride (0.54 cm^3, 5.68 mmol) at room temp. The reaction mixture was stirred for 12 h and poured into saturated aq. NH_4Cl (5 cm^3).

The aqueous phase was extracted with CH_2Cl_2 (3 × 5 cm^3) and the combined extracts were washed with brine (2 × 2 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification through flash column chromatography [hexane–diethyl ether (1 : 1 v/v)] provided the *keto ester* **12** (0.64 g, 89%) as an oil (a 1 : 1 mixture of diastereoisomers) R_f 0.35 [diethyl ether–hexane (3 : 1 v/v)]; ν_{max}/cm^{-1} 1739 (ester C=O) and 1668 (enone C=O); δ_H(*inter alia*) 1.08 (1.5 H, s, 8-Me) and 1.10 (1.5 H, s, 8-Me); *m/z* (EI) 381 (1.5%, MH^+) (Found: C, 63.0; H, 7.6. $C_{20}H_{28}O_5S$ requires C, 63.2; H, 7.4%).

7β-*Acetoxy*-4,8β,13-*trimethyl*-19-*norpodocarpa*-3,12-*dien*-14-*one* **3**.—A solution of the ester **12** (0.3 g) and Methylene Blue (1 mg) in dry benzonitrile (80 cm^3) was heated under reflux for 110 h. After the reaction mixture had cooled to room temp., the solvent was removed under reduced pressure. Purification by flash column chromatography [hexane–diethyl ether (7 : 1 v/v)] afforded the *title compound* **3** (0.15 g, 62%) as a solid, m.p. 135–137 °C (lit.,[17] 138–140 °C); R_f 0.33 [hexane–diethyl ether (3 : 1 v/v)]; $[\alpha]_D^{21}$ +92.5 (*c* 3.8, EtOH) {lit.,[17] $[\alpha]_D^{23}$ +89.8 (*c* 0.6, EtOH)}; ν_{max}/cm^{-1} 1736 (ester C=O) and 1678 (enone C=O); δ_H 0.93 (3 H, s), 1.24 (3 H, s), 1.2–1.9 (11 H, m), 2.05 (3 H, m), 2.09 (3 H, s), 2.39 (2 H, m), 5.18 (1 H, dd, *J* 12 and 4.8), 5.32 (1 H, br) and 6.60 (1 H, br); *m/z* (EI) 316 (17.8%, M^+).

12α,13α-*Epoxy*-7β-*hydroxy*-4,8β,13β-*trimethyl*-19-*norpodocarp*-3-*en*-14-*one* **13**.—To a solution of the enone **3** (0.5 g, 1.58 mmol) in THF (15 cm^3) was added a solution of Triton B (40%; 1.58 cm^3) in methanol followed by addition of an aqueous solution of *tert*-butyl hydroperoxide (70%; 1.58 cm^3) at room temp. The reaction mixture was stirred for 20 h and the solvent was removed under reduced pressure. The residue was extracted with diethyl ether (3 × 10 cm^3) and the combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure. A solution of KOH (0.5 g) in methanol (5 cm^3) was added to the residue. The reaction mixture was stirred for 24 h at room temp. and was then concentrated. The residue was acidified with aq. HCl (10% v/v; 5 cm^3) and extracted with diethyl ether (3 × 10 cm^3). The combined extracts were washed with brine (5 cm^3), dried ($MgSO_4$), and concentrated. Purification by flash chromatography [hexane–diethyl ether (4 : 1 v/v)] afforded the *title compound* **13** (0.47 g, 85%) as a solid, m.p. 112–113 °C (lit.,[17] 110–112 °C); R_f 0.23 [hexane–diethyl ether (3 : 1 v/v)]; $[\alpha]_D^{22}$ +4.4 (*c* 0.4) {lit.,[17] $[\alpha]_D$ +4.2 (*c* 1.0)}; ν_{max}/cm^{-1} 3549 (OH) and 1698 (ketone C=O); δ_H 0.86 (3 H, s), 1.18 (3 H, s), 1.46 (3 H, s), 1.65 (3 H, s), 0.9–1.8 (5 H, m), 2.00 (5 H, m), 2.36 (1 H, ddd, *J* 14, 3.5 and 2.5), 3.41 (1 H, br), 3.95 (1 H, dd, *J* 9 and 3.5) and 5.31 (1 H, b); *m/z* (EI) 290 (11.7%, M^+).

12α,13α-*Epoxy*-7α-*hydroxy*-4,8β,13β-*trimethyl*-19-*norpodocarp*-3-*en*-14-*one* **15**.—To a solution of the β-alcohol **13** (0.17 g, 0.59 mmol), pyridine (0.47 cm^3, 5.86 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (8 cm^3) was added Tf_2O (0.49 cm^3, 2.93 mmol) at room temp. The reaction mixture was stirred for 24 h and poured into saturated aq. NH_4Cl (2 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 cm^3). The combined extracts were washed with brine (2 × 2 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography (CH_2Cl_2) provided the triflate **14** as a solid, m.p. 102–103 °C; R_f 0.67 (CH_2Cl_2).

The triflate **14** was dissolved in wet DMF (10 cm^3) and the reaction mixture was stirred for 48 h at room temp. The solvent was removed under reduced pressure and a solution of K_2CO_3 (0.3 g) in methanol (5 cm^3) was added to the residue. The reaction mixture was stirred for 24 h at room temp. and was then concentrated. The residue was acidified with aq. HCl (10% v/v; 5 cm^3) and extracted with CH_2Cl_2 (4 × 5 cm^3). The combined extracts were washed with brine (2 cm^3), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (CH_2Cl_2) afforded the *title compound* **15** (103 mg, 60%) as needles, m.p. 105–106 °C; R_f 0.23 (CH_2Cl_2); $[\alpha]_D^{23}$ −72.0 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 3557 (OH) and 1701 (ketone C=O); δ_H 0.85 (3 H, s), 1.08 (3 H, s), 1.23 (1 H, m), 1.45 (3 H, s), 1.55 (2 H, m), 1.64 (3 H, s), 1.74 (1 H, dt, *J* 12.5 and 5), 2.00 (5 H, m), 2.39 (1 H, dd, *J* 13.2 and 3.9), 2.55 (1 H, br d, *J* 13.2), 3.39 (1 H, br), 4.19 (1 H, t, *J* 3.9) and 5.31 (1 H, br); *m/z* (CI, NH_3) 308 (100%, MNH_4^+) (Found: C, 74.2; H, 9.1. $C_{18}H_{26}O_3$ requires C, 74.5; H, 9.0%) (Found: MNH_4^+, 308.2231. $C_{18}H_{30}NO_3$ requires M, 308.2226).

7α-*Acetoxy*-12α,13α-*epoxy*-4,8β,13β-*trimethyl*-19-*norpodocarp*-3-*en*-14-*one* **16**.—To a solution of the α-alcohol **15** (0.1 g, 0.35 mmol), pyridine (0.17 cm^3, 2.10 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (4 cm^3) was added Ac_2O (0.1 cm^3, 1.04 mmol) at room temp. The reaction mixture was stirred for 24 h and poured into saturated aq. NH_4Cl (1 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 2 cm^3) and the combined extracts were washed with brine (2 × 1 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [hexane–diethyl ether (4 : 1 v/v)] provided the *title compound* **16** (0.11 g, 100%) as needles, m.p. 149–150 °C; R_f 0.71 [diethyl ether–CH_2Cl_2 (1 : 20 v/v)]; $[\alpha]_D^{21}$ −54.9 (*c* 0.43); ν_{max}/cm^{-1} 1742 (ester C=O) and 1711 (ketone C=O); δ_H 0.85 (3 H, s), 1.11 (3 H, s), 1.26 (1 H, m), 1.41 (3 H, s), 1.60 (3 H, s), 1.50–1.52 (2 H, m), 1.79 (1 H, dt, *J* 12.5 and 4.5), 2.00 (3 H, s), 1.88–2.20 (4 H, m), 2.38 (2 H, m), 3.39 (1 H, br) and 5.32 (2 H, br); *m/z* (CI, NH_3) 350 (100%, MNH_4^+) (Found: C, 72.3; H, 8.6. $C_{20}H_{28}O_4$ requires C, 72.3; H, 8.4%) (Found: MNH_4^+, 350.2346. $C_{20}H_{32}NO_4$ requires M, 350.2331).

12α,13α-*Epoxy*-14β-*hydroxypicras*-3-*en*-16-*one* **17**.—To a solution of diisopropylamine (12.7 mm^3, 0.09 mmol) in dry THF (0.3 cm^3) under nitrogen was added 1.6 mol dm^{-3} butyllithium in hexane (56.3 mm^3, 0.09 mmol) at −78 °C. After the reaction mixture had been stirred for 10 min at −78 °C, a solution of compound **16** (20 mg, 0.06 mmol) in THF (0.15 cm^3) containing DMPU (0.15 cm^3) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C and was then warmed up to 0 °C. After 30 min at 0 °C, the reaction mixture was quenched with saturated aq. NH_4Cl (0.5 cm^3). The aqueous phase was extracted with CH_2Cl_2 (4 × 5 cm^3). The combined extracts were washed with brine (2 × 0.5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [hexane–diethyl ether (1 : 2 v/v)] yielded the *title compound* **17** (19 mg, 98%) as needles, m.p. 263–264 °C; R_f 0.31 [diethyl ether–hexane (4 : 1 v/v)]; $[\alpha]_D^{20}$ +26.7 (*c* 0.21); ν_{max}/cm^{-1} 3687 (OH) and 1728 (lactone C=O); δ_H 0.90 (3 H, s), 1.12 (3 H, s), 1.29 (1 H, dd, *J* 12.5 and 4.9), 1.38 (3 H, s), 1.50–1.68 (6 H, m), 1.82 (1 H, dd, *J* 12 and 2.5), 1.88 (1 H, dd, *J* 12 and 2.5), 2.01 (2 H, br), 2.11 (1 H, dt, *J* 14.5 and 3), 2.18 (1 H, dd, *J* 15 and 4.5), 2.26 (1 H, br d, *J* 15), 2.61 (1 H, d, *J* 18), 3.22 (1 H, br), 3.28 (1 H, d, *J* 18), 4.68 (1 H, t, *J* 3) and 5.35 (1 H, br); *m/z* (CI, NH_3) 350 (100%, MNH_4^+) (Found: C, 72.8; H, 8.8. $C_{20}H_{28}O_4$ requires C, 72.3; H, 8.4%) (Found: MNH_4^+, 350.2360. $C_{20}H_{32}NO_4$ requires M, 350.2331).

12α,13α-*Epoxypicrasa*-3,14-*dien*-16-*one* **18**.—To a solution of compound **17** (25 mg, 0.08 mmol) in pyridine (1.5 cm^3) was added $SOCl_2$ (0.2 cm^3) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and was then concentrated. The residue was dissolved in CH_2Cl_2 (10 cm^3) and the organic phase was washed with brine (2 × 1 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash column

chromatography [hexane–diethyl ether (1 : 1 v/v)] yielded the *title compound* **18** (23 mg, 98%) as needles, m.p. 145–146 °C; R_f 0.34 [diethyl ether–hexane (3 : 1 v/v)]; $[\alpha]_D^{20}$ −105.7 (*c* 0.28); ν_{max}/cm^{-1} 1720 (conjugated lactone C=O); δ_H 0.88 (3 H, s), 1.20 (3 H, s), 1.42 (1 H, dd, *J* 12.5 and 5.2), 1.56 (3 H, s), 1.60 (1 H, m), 1.66 (3 H, s), 1.73 (1 H, td, *J* 14.2 and 3), 1.87 (1 H, dd, *J* 12 and 3), 1.92 (1 H, dd, *J* 12 and 3), 2.00 (2 H, br), 2.19 (1 H, dt, *J* 14.2 and 3), 2.27 (1 H, dd, *J* 15 and 5.2), 2.33 (1 H, br d, *J* 15), 3.28 (1 H, d, *J* 2.5), 4.37 (1 H, t, *J* 3), 5.38 (1 H, br) and 6.12 (1 H, s); *m/z* (CI, NH_3) 315 (100%, MH^+) (Found: C, 76.5; H, 8.5. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%) (Found: M^+, 314.1872. $C_{20}N_{26}O_3$ requires M, 314.1881).

12α,13α-*Epoxypicras*-3-*en*-16-*one* **22** *and* 12α-*Hydroxypicrasa*-3,13-*dien*-16-*one* **23**.—To a stirred solution of the α,β-unsaturated lactone **18** (28 mg, 0.09 mmol) and $NiCl_2 \cdot 6H_2O$ (1 mg) in methanol (2 cm^3) at −25 °C was added sodium boranuide (7 mg, 0.18 mmol) in small batches over a period of 10 min. The reaction mixture was stirred for 30 min at −25 °C and quenched with saturated aq. NH_4Cl (1 cm^3). The aqueous phase was extracted with CH_2Cl_2 (4 × 3 cm^3) and the combined extracts were washed with brine (2 × 1 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [light petroleum–diethyl ether (1 : 4 v/v)] yielded the isomeric *title compounds* **22** and **23** in the ratio of 1 : 3, respectively (20 mg, 70%).

Compound **22**: a solid, m.p. 155–156 °C; R_f 0.60 [light petroleum–diethyl ether (1 : 3 v/v)]; $[\alpha]_D^{22}$ +8.6 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 1734 (lactone C=O); δ_H 0.88 (3 H, s), 1.08 (1 H, m), 1.16 (3 H, s), 1.24 (1 H, dd, *J* 13 and 4.5), 1.36 (3 H, s), 1.58 (1 H, m), 1.62 (1 H, m), 1.63 (3 H, s), 1.69 (1 H, dt, *J* 13 and 2.2), 1.77 (1 H, td, *J* 13 and 3), 1.92 (1 H, dd, *J* 12 and 7), 1.99 (1 H, m), 2.50 (1 H, td, *J* 13 and 2), 2.18 (1 H, dt, *J* 13 and 4.5), 2.28 (1 H, dd, *J* 15 and 2.2), 2.59 (1 H, dd, *J* 19 and 7), 2.79 (1 H, dd, *J* 19 and 12), 3.26 (1 H, dd, *J* 4.5 and 3), 4.30 (1 H, t, *J* 2.2) and 5.33 (1 H, t, *J* 2.2); *m/z* (CI, NH_3) 317 (16%, MH^+) (Found: M^+, 316.2052. $C_{20}H_{28}O_3$ requires M, 316.2038).

Compound **23**: needles, m.p. 178–179 °C; R_f 0.34 [hexane–diethyl ether (1 : 3 v/v)]; $[\alpha]_D^{22}$ +9.4 (*c* 0.17); ν_{max}/cm^{-1} 3281 (OH) and 1745 (lactone C=O); δ_H 0.79 (3 H, s), 1.09 (3 H, s), 1.52 (4 H, m), 1.65 (3 H, s), 1.78 (3 H, s), 1.79 (1 H, m), 1.92 (1 H, dd, *J* 14.7 and 3), 2.05 (2 H, m), 2.14 (1 H, dd, *J* 14.7 and 6.8), 2.21 (1 H, dd, *J* 15 and 3), 2.32 (1 H, db, *J* 15), 3.12 (1 H, d, *J* 14.5), 3.39 (1 H, d, *J* 14.5), 4.13 (1 H, br), 4.30 (1 H, t, *J* 3) and 5.36 (1 H, br); *m/z* (EI) 316 (66.4%, M^+) (Found: C, 75.4; H, 9.3%; M^+, 316.2016. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%).

Picrasa-3,12,14-*trien*-16-*one* **24** *and* 12α-*Hydroxypicrasa*-3,13-*dien*-16-*one* **23**.—To a solution of the α,β-unsaturated lactone **18** (20 mg, 0.064 mmol) in acetic acid (0.5 cm^3) was added an excess of zinc powder. The reaction mixture was stirred under reflux for 24 h. After the reaction mixture had been cooled to room temp., water (1 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (4 × 3 cm^3) and the combined extracts were washed with brine (2 × 0.5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [hexane–diethyl ether (1 : 1 v/v)] yielded the *title compounds* **24** and **23** in the ratio 1 : 19, respectively (12 mg, 60%).

Compound **24**: an oil, R_f 0.78 [hexane–diethyl ether (1 : 3 v/v)]; ν_{max}/cm^{-1} 1709 (conjugated lactone C=O); δ_H 0.89 (3 H, s), 1.15 (3 H, s), 1.60 (2 H, br), 1.67 (3 H, s), 1.79 (2 H, m), 1.87 (3 H, s), 2.01 (2 H, br), 2.30 (4 H, m), 4.36 (1 H, t, *J* 2.8), 5.38 (1 H, br), 5.72 (1 H, s) and 5.81 (1 H, br); *m/z* (EI) 298 (17.2%, M^+) (Found: M^+, 298.1917. $C_{20}H_{26}O_2$ requires M, 298.1933).

Picrasa-3,14-*diene*-12,16-*dione* **25**.—To a suspension of the allylic alcohol **23** (12 mg, 0.038 mmol) and 3 Å molecular sieves powder (0.1 g) in dry CH_2Cl_2 (2 cm^3) was added PCC (12.3 mg, 0.057 mmol) at room temp. The reaction mixture was stirred for 24 h, diluted with diethyl ether (10 cm^3), and filtered through a short column of silica gel. The column was washed with diethyl ether (10 cm^3). The combined eluent was washed with brine (2 × 2 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [light petroleum–diethyl ether (5 : 1 v/v)] afforded the *title compound* **25** (11 mg, 91%) as needles, m.p. 230–231 °C; R_f 0.50 [hexane–diethyl ether (1 : 3 v/v)]; $[\alpha]_D^{20}$ +89.1 (*c* 0.22); ν_{max}/cm^{-1} 1749 (lactone C=O) and 1659 (enone C=O); δ_H 0.90 (3 H, s), 1.22 (3 H, s), 1.58 (3 H, s), 1.66 (2 H, s), 1.80 (3 H, s), 1.87 (1 H, dd, *J* 14.8 and 3), 1.93 (1 H, dd, *J* 11.5 and 6), 2.05 (2 H, br), 2.29 (1 H, dt, *J* 15 and 3), 2.40 (1 H, br d, *J* 15), 2.56 (2 H, m), 3.36 (1 H, dd, *J* 15 and 1.5), 3.60 (1 H, d, *J* 15), 4.38 (1 H, t, *J* 3) and 5.49 (1 H, b); *m/z* (CI, NH_3) 315 (61.4%, MH^+) (Found: C, 76.6; H, 8.3%; M^+, 314.1874. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; M, 314.1881).

Picrasa-3,12-*dien*-16-*one* **2**.—To a solution of the enone **25** (10 mg, 0.032 mmol) in absolute ethanol (0.3 cm^3) was added tosylhydrazine (7.1 mg, 0.038 mmol) at room temp. The reaction mixture was stirred at 70 °C for 12 h. After the reaction mixture was cooled to room temp., water (1 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (4 × 3 cm^3) and the combined extracts were washed with brine (2 × 0.5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [CH_2Cl_2–diethyl ether (25 : 1 v/v)] yielded the tosylhydrazone derivative **26** as an oil.

Compound **26** was dissolved in acetic acid (0.5 cm^3) and sodium cyanoboranuide (7 mg, 0.11 mmol) was added in small batches during 10 min. The reaction mixture was stirred at 70 °C for 12 h. After the reaction mixture had cooled to room temp., water (1 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (6 × 3 cm^3) and the combined extracts were washed with brine (2 × 0.5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by purification through flash column chromatography [light petroleum–diethyl ether (1 : 1 v/v)] yielded the *title compound* **2** (4.8 mg, 50%) as an oil, R_f 0.17 [light petroleum–diethyl ether (1 : 1 v/v)]; $[\alpha]_D^{20}$ +10.5 (*c* 0.46); ν_{max}/cm^{-1} 1732 (lactone C=O); δ_H 0.85 (3 H, s), 1.06 (3 H, s), 1.49 (1 H, dd, *J* 11.5 and 6), 1.55 (3 H, s), 1.58–1.70 (7 H, m), 1.77 (1 H, td, *J* 14 and 2.5), 1.89 (1 H, dd, *J* 12 and 7), 1.49–2.40 (4 H, m), 2.27 (1 H, dd, *J* 19 and 12), 2.82 (1 H, dd, *J* 19 and 7), 4.35 (1 H, t, *J* 3), 5.30 (1 H, br) and 5.36 (1 H, br); *m/z* (EI) 300 (94.9%, M^+) (Found: M^+, 300.2068. $C_{20}H_{28}O_2$ requires M, 300.2089).

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