

## Synthesis of an Alberta Oil Sand Bitumen C<sub>20</sub> Tricyclic Carboxylic Acid bearing a Novel Diterpenoid Skeleton

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The synthesis of (±)-13-norisocopalane-15-carboxylic acid (**9**), for comparison with the C<sub>20</sub> carboxylic acid found in Alberta oil sand bitumen, is described. It involves the preparation of the key intermediate (±)-methyl 16-norisocopalane-15-oate (**27**), by transformation of the known allylic alcohol (**20**), and homologation of (**27**) *via* the nitrile (**30**). Comparison of natural and synthetic methyl ester derivatives unequivocally established the correctness of the structure (**9**) for the natural product.

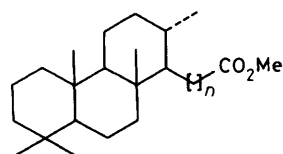
Tricyclic saturated terpene hydrocarbons constitute an important class of biomarkers of widespread occurrence in petroleum and sediments.<sup>1,2</sup> Recently, a new series of related tricyclic carboxylic acids (C<sub>20</sub> to C<sub>26</sub>) from the Alberta oil sand deposits was identified (as methyl esters). These compounds could be considered as geochemical precursors of the tricyclic terpenes, even though geochemical decarboxylations alone are not sufficient to explain the full range (C<sub>19</sub> to C<sub>45</sub>) and distribution of the latter.<sup>3</sup>

The structures of the carboxylic acids from C<sub>21</sub> to C<sub>26</sub> [(**1**)–(**6**)] were determined by their transformation into the corresponding hydrocarbons and comparison with the natural terpenes, isolated from the oil sand deposits. The hydrocarbon obtained from the methyl ester of the C<sub>20</sub> carboxylic acid, however, did not correspond to the tricyclic terpene (**7**); furthermore, the natural ester did not match any of the four possible isomers at C-13 and C-14 of the ester (**8**). On the basis of this evidence and the information obtained from the mass spectral fragmentation pattern of the C<sub>20</sub> ester and the corresponding alkane, the novel structures (**10**) and (**11**) were proposed.<sup>3</sup> In order to identify fully the natural carboxylic acid, we decided to synthesize the proposed structure (**9**),<sup>4</sup> as a continuation of our studies on the partial syntheses of biological markers.<sup>5</sup> Our approach was to select a readily available starting material that could be transformed, by simple functional group interconversions, into the target molecule.

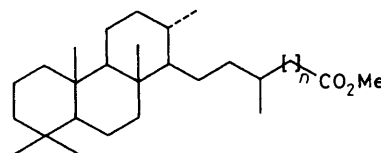
We reasoned that the readily available tricyclic enone (**12**)<sup>6–8</sup> would fulfil our requirements if a 1,4-conjugate addition, with simultaneous trapping of the corresponding enolate by an adequate electrophile, could be carried out.

Preliminary experiments to establish the stereochemical preference of the conjugated addition indicated, in agreement with a report for a related system,<sup>9</sup> the low reactivity of (**12**) towards lithium dimethylcuprate. In fact, from the reaction mixture of (**12**) and the cuprate, under standard conditions, 60% of the starting ketone was recovered; the remaining components of the mixture were characterized as the allylic alcohols (**13**) (6%) and (**14**) (12%), and the saturated ketone (**15**) (10%). Use of the crystalline copper bromide–dimethyl sulphide complex,<sup>10</sup> catalysis by boron trifluoride–ether complex,<sup>11</sup> or a copper iodide–Grignard reagent did not improve the reaction performance. The ketone (**15**) was produced by conjugate addition from the less hindered  $\alpha$ -face of (**12**), as shown by a comparative <sup>13</sup>C n.m.r. spectral analysis of the former and the known ketone (**16**).<sup>12</sup>

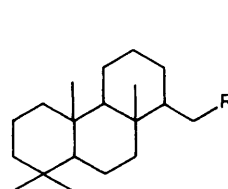
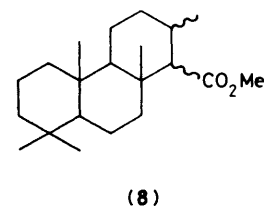
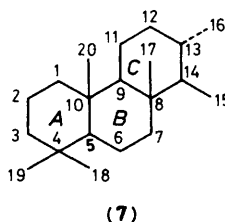
We ruled out use of the known hydroxy ester (**17**), a potentially good starting material, since it is obtained in only 5–10% yield by acid-catalysed cyclization of the tetraene (**18**).<sup>8</sup>



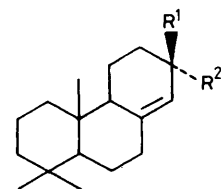
- (1) C<sub>21</sub>, n = 1  
 (2) C<sub>22</sub>, n = 2  
 (3) C<sub>23</sub>, n = 3



- (4) C<sub>24</sub>, n = 4  
 (5) C<sub>25</sub>, n = 5  
 (6) C<sub>26</sub>, n = 6



- (9) R = CO<sub>2</sub>H  
 (10) R = CO<sub>2</sub>Me  
 (11) R = CH<sub>3</sub>



- (12) R<sup>1</sup> R<sup>2</sup> = O  
 (13) R<sup>1</sup> = Me, R<sup>2</sup> = OH  
 (14) R<sup>1</sup> = OH, R<sup>2</sup> = Me

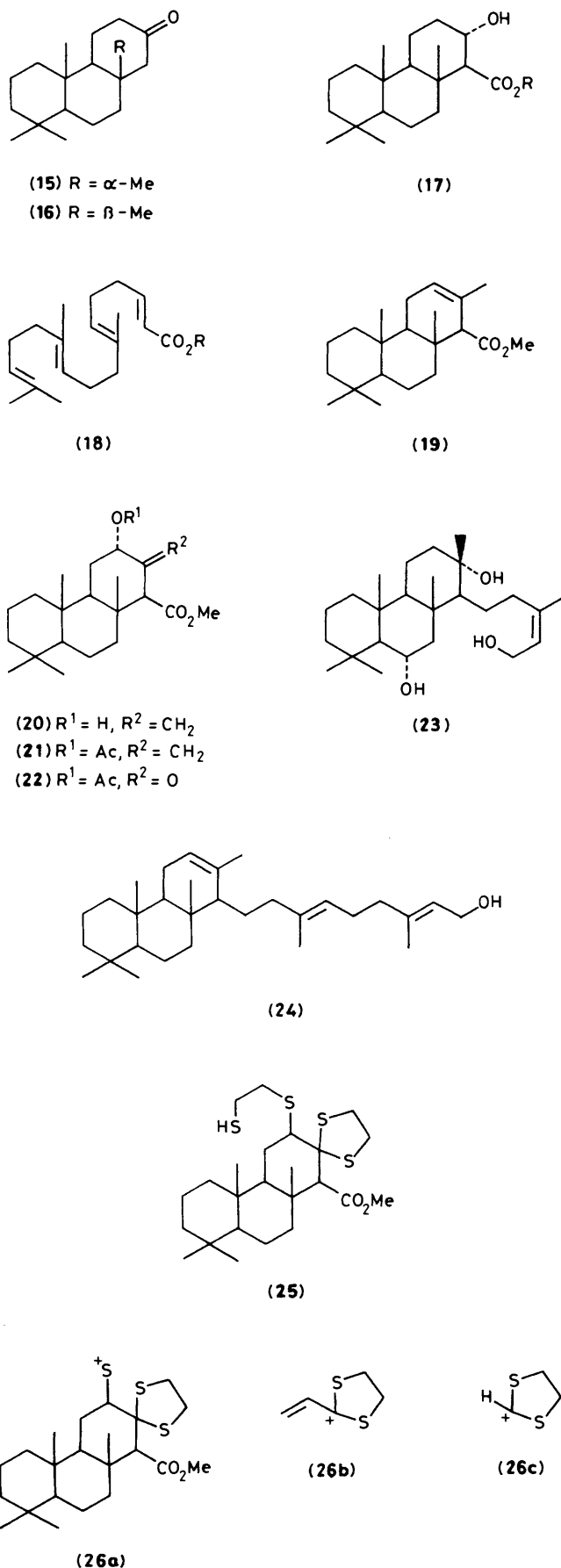
In view of the foregoing results, we decided to study the transformation of the readily available methyl isocopalate (19)<sup>14</sup> into the desired tricyclic carboxylic acid (9). On the basis of our previous experience,<sup>15</sup> we expected that the transformation of (19) into the key intermediate (20) could be carried out in good overall yield. Cleavage of the exocyclic double bond of (20) followed by reduction of the oxygenated functional groups of ring C, after or before the homologation of the side chain, would give (9).

In practice, the hydroxy ester (20) was transformed into the related acetate (21), in order to prevent the formation of abnormal products during the exocyclic double-bond cleavage step.<sup>16</sup> Ozonolysis of (21) followed by reductive work-up afforded the  $\beta$ -oxo ester (22) in 78% yield. The <sup>1</sup>H n.m.r. spectrum revealed that (22) exists as an equilibrium mixture of keto and enol forms, with the C-12 acetate group in the axial position, on the basis of the coupling constant of the C-12 proton resonance [ $\delta$  5.08 and 5.40\* (t,  $J$  3 Hz)]. The <sup>13</sup>C n.m.r. spectrum confirmed the foregoing observations, and the signal at 52.1 p.p.m., attributed to C-9, indicated that the methoxy-carbonyl group remains equatorial, as in (21), probably owing to strong *syn* axial-axial repulsion between an axial C-14 substituent and the C-12 acetoxy group.

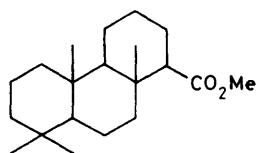
Thus, it was hoped that alkylation of the enolate of the  $\beta$ -oxo ester with ethyl bromoacetate, followed by hydrolysis of the product, decarboxylation of the remaining  $\beta$ -oxo acid moiety, and subsequent esterification of the resultant  $\gamma$ -oxo acid would yield the homologous oxo ester. The synthesis of (9) through this route was considered highly desirable and of broad scope, because it could enable the introduction of different side chains, such as those present in cheilantatriol (23) and tricyclohexaprenol (24), the postulated C<sub>30</sub> precursor of the petroleum tricyclic saturated terpenes.<sup>17</sup>

Unfortunately, this transformation failed; recovery of starting material was almost quantitative. This failure may be attributed to the sterically encumbered environment at C-14 in the enolate, in agreement with a previous report of a sterically similar bicyclic compound.<sup>8</sup>

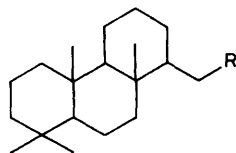
Attempts to achieve reduction deacetoxylation of (22) with zinc in refluxing acetic acid led only to a mixture of starting material and some decomposition products. However, when (22) was treated with ethanedithiol and boron trifluoride-ether, under the standard conditions for a thioacetalization, a crystalline solid was obtained in 75% yield. The latter was formulated as the unexpected compound (25) on the basis of its spectroscopic characteristics. It gave a molecular ion at  $m/z$  488 in the mass spectrum, together with an  $m/z$  427 signal due to  $M - [\text{CH}_2]_2\text{SH}$  (26a), an  $m/z$  131 base peak attributed to (26b), and a minor fragment ion at  $m/z$  105 (26c). Interestingly, the  $m/z$  191 ion, a typical feature for this kind of compound, showed a relative abundance of only 9%. In the <sup>1</sup>H n.m.r. spectrum, a multiplet at  $\delta$  2.33–3.53 revealed the presence of 11 protons, assigned to the C-12 and C-13 substituents, together with the C-12 and C-14 protons. That the displacement of the acetoxy group occurred with complete inversion of configuration was shown by a comparative <sup>13</sup>C n.m.r. spectral analysis of (25) and (22). As expected, removal of the axial acetoxy group at C-12 induces a deshielding effect of 5.6 p.p.m. at C-9 in going from (22) to (25). Fieser *et al.*<sup>18</sup> reported the isolation of similar abnormal products in the condensation of acetoxy ketones with ethanedithiol, in a vinylogous related system,



\* Since the sample of copalic acid used for the preparation of methyl isocopalate was racemic, the structures of all intermediates and final products are written without regard for their absolute configurations. The isolation of ( $\pm$ )-copalic acid from *Eperua purpurea* was recently reported.<sup>13</sup>



(27)



(28) R = OH

(29) R = OMs

(30) R = CN

(31) R = H

during thioacetalization experiments. These authors proposed a carbocation-mediated process to rationalize these observations; however, this mechanism would explain the inversion of the configuration at C-12 only on the basis of the formation of the more stable, equatorial product.

Thus the foregoing reaction led to simultaneous deoxygenation at C-12 and C-13; treatment of (25) with Raney nickel afforded (27) in good overall yield.

Our first approach to the synthesis of (9) from (27), by direct one-pot homologation of the latter under the conditions described by Kowalski *et al.*,<sup>19</sup> failed. We therefore turned to the classical nitrile-mediated one-carbon homologation, in spite of the rather long route involved.

In order to obtain a more convenient functional group for lengthening the side chain, the methyl ester (27) was reduced to the alcohol (28), with lithium aluminium hydride in ether, and (28) was transformed into the nitrile (30) *via* the methane-sulphonate (29), by displacement with sodium cyanide in dimethyl sulphoxide.

We then needed to convert (30) into the C<sub>20</sub> carboxylic acid. Preliminary attempts directed towards hydrolysis of the nitrile group were not encouraging: (30) was not attacked under various conditions, such as treatment with alkaline hydrogen peroxide, 3 days reflux of the nitrile in butanol containing 10% sodium hydroxide, or heating at 160 °C with 4M potassium hydroxide in diethylene glycol-water (8:1) for 10 days. Furthermore, the nitrile (30) resisted the conditions for hydrolysis catalysed by phosphoric acid<sup>20</sup> or sulphuric acid,<sup>21</sup> and the Pinner reaction (acid-catalysed alcoholysis of nitriles<sup>22</sup>) was of uncertain value, leading to oily solvent-immiscible drops containing an inseparable mixture of ester (10) and starting material, as shown by the 1 730 cm<sup>-1</sup> i.r. absorption and a small <sup>1</sup>H n.m.r. singlet at 3.70 p.p.m. Suspecting a low solubility effect, we changed the solvent system; the results, however, were not improved.

Fortunately, under more drastic conditions of temperature and alkali concentration, as described by Wenkert *et al.*,<sup>23</sup> the nitrile smoothly afforded the acid (9) in good yield. Conversion of (9) into (10) was achieved quantitatively by treatment with ethereal diazomethane.

It may be argued that the notable lack of reactivity of (30) arises from a steric factor, which can be expressed in terms of the rule of six,<sup>24</sup> *viz.* that the greater the number of atoms at the sixth position from the centre of interest (the nitrogen in this case), the more difficult becomes addition to the multiple bond. In this sense, (30) which has six atoms at the sixth positions, is expected to be resistant to hydrolysis.

Natural and synthetic tricyclic methyl esters, were compared by mass spectroscopy and g.l.c. Chromatography of (10) and a petroleum extract containing the natural product on capillary columns coated with two stationary phases of different polarities (DB-1 and DB-5) gave identical retention times, as shown by flame ionization detection. On the other hand, co-injection of the samples into a gas chromatography-mass spectrometry single-ion recording system (at *m/z* 123 and 191)

led to their co-elution, and the two compounds displayed identical mass spectra.

The natural product (9) is, as far as we know, the first C<sub>20</sub> diterpenoid compound bearing the uncommon carbon skeleton (11) to be discovered, synthesized, and characterized. However, being a diterpenoid, on the basis of its carbon number and general features, the skeleton of (9) does not follow the isoprene rule.

Since it may be a degradation product, compound (9) does not necessarily have only one origin; nevertheless, the simultaneous discovery of the carboxylic acid related to the ester (1) may constitute an explanation of the presence of the tricyclic acid in this degraded oil, in view of the relatively common occurrence of demethylations in organic materials from geological sources. If we accept current theories of diagenetic decarboxylation as a source of petroleum hydrocarbons, compound (9) might be the geological precursor of the known and ubiquitous compound (31).<sup>25</sup> Moreover, as previously suggested, tricyclic terpene carboxylic acids are probably formed from the corresponding hydrocarbons; thus, the demonstration of the presence of (9) in oils may constitute a strong indication of the existence of the as yet undiscovered hydrocarbon (11) or, conversely, the observation of the latter in degraded oils may be a confirmation of the foregoing hypothesis, and another example of the predictive aspects of geochemical studies, allowing one to build up a better picture of the degradative processes in sediments.<sup>17</sup>

## Experimental

M.p.s were determined with an Ernst Leitz hot-stage apparatus, i.r. spectra were recorded with a Beckman Acculab 8 spectrometer, and <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra were recorded at 80.13 and 20.15 MHz, respectively, with a Bruker WP 80 SY spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. The carbon chemical shifts were assigned by comparison with the reported data of (20) and related products,<sup>15</sup> and analysis of the generated CH/CH<sub>3</sub> and CH<sub>2</sub>/q subspectra by use of the spin-echo sequence and the attached proton test (APT).<sup>26</sup> All solvents were purified and dried by standard techniques. All reactions were performed under dry nitrogen. Column chromatography was performed on silica gel 60H, slurry-packed, run under a low pressure of nitrogen, with increasing amounts of ether in hexane as solvent. 'Ether' refers to diethyl ether.

**Reaction of Lithium Dimethylcuprate with the Enone (12).**—To a gently stirred solution of lithium dimethylcuprate, prepared at -78 °C from copper(I) iodide (155.4 mg, 0.82 mmol) and 1.518M methyl-lithium (1.07 ml, 1.62 mmol) in ether (6 ml), a solution of enone (12) (100 mg, 0.407 mmol) in ether (2 ml) was added dropwise. The mixture was stirred for 1 h, then saturated aqueous ammonium chloride (10 ml) was added, and the products were extracted with ether (3 × 25 ml). The combined extracts were dried and evaporated, and the resulting oil was chromatographed, yielding the *ketone* (15) (11 mg, 0.042 mmol; 10%), m.p. 135–136 °C (from MeOH); *v*<sub>max</sub>. 2 950, 2 870, 1 715, 1 470, and 1 370 cm<sup>-1</sup>; *δ*<sub>H</sub> 0.88 (6 H, s), 0.92 (3 H, s), and 1.10 (3 H, s, 17-H); *δ*<sub>C</sub> 211.8 (C-13), 55.0 (C-5), 53.2 (C-9), 50.6 (C-14), 41.8 (C-3), 41.8 (C-12), 38.6 (C-10), 38.4 (C-1), 38.4 (C-8), 33.5 (C-18), 33.2 (C-4), 32.0 (C-17), 21.7 (C-19), 20.6 (C-11), 18.6 (C-6), 18.5 (C-2), and 17.4 (C-20); *m/z* 262 (*M*<sup>+</sup>, 11%), 247 (22), 229 (16), 206 (25), 191 (3), 177 (3), 163 (3), 149 (6), 136 (11), 123 (43), 111 (91), 109 (42), 95 (47), 81 (61), 55 (80), and 41 (100).

Further elution gave the *enol* (14) (6 mg, 0.022 mmol; 6%); *δ*<sub>H</sub> 0.78 (3 H, s), 0.85 (3 H, s), 0.88 (3 H, s), 1.24 (3 H, s, 16-H), and 5.43 (1 H, br s, 14-H).

Increase in solvent polarity afforded the starting enone (12)

(60 mg, 0.244 mmol; 60%), followed by the *enol* (**13**) (12 mg, 0.046 mmol; 12%), m.p. 112–114 °C (from hexane);  $\nu_{\max}$  (KBr) 3 400 (alcohol), 2 940, 2 860, 1 470, 1 370, 1 140, and 1 070  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.75 (3 H, s), 0.85 (3 H, s), 0.88 (3 H, s), 1.24 (3 H, s, 16-H), and 5.37 (1 H, br s, 14-H);  $\delta_{\text{C}}$  138.8 (C-8), 129.1 (C-14), 69.4 (C-13), 54.6 (C-5), 50.7 (C-9), 42.0 (C-3), 39.0 (C-12), 38.2 (C-10), 38.0 (C-1), 35.4 (C-7), 33.5 (C-18), 33.2 (C-4), 27.9 (C-16), 22.3 (C-6), 22.0 (C-19), 19.9 (C-11), 18.8 (C-2), and 14.6 (C-20);  $m/z$  262 ( $M^+$ , 2%), 247 (23), 229 (11), 188 (2), 175 (3), 159 (4), 147 (4), 137 (43), 123 (30), 108 (63), 95 (30), 81 (43), 69 (35), 55 (47), 43 (100), and 29 (29).

(±)-*Methyl 16-Norisocopalan-15-oate* (**27**).—Acetic anhydride (1.8 ml), was added to the hydroxy ester (**20**) (645 mg, 1.93 mmol) (m.p. 152–154.5 °C; lit.,<sup>15</sup> 152–154 °C) dissolved in pyridine (2 ml). The mixture was left overnight at room temperature, water (4 ml) was added, and the two-phase system was stirred for 4 h. An excess of 20% hydrochloric acid was added and the solution was extracted with ether (3 × 30 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (10 ml) and brine (2 × 20 ml), then dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The residue was filtered through a short column of silica, affording the *acetate* (**21**) (689 mg, 1.83 mmol; 95%), m.p. 90–91.5 °C (from MeOH);  $\nu_{\max}$  (KBr) 3 020–2 880, 1 735, 1 660, 1 445, 1 375, 1 245, 1 170, 1 050, 1 020, and 930  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.81 (3 H, s), 0.83 (3 H, s), 0.86 (3 H, s), 1.03 (3 H, s), 2.06 (3 H, s, acetate), 3.17 (1 H, br s, 14-H), 3.65 (3 H, s,  $\text{OCH}_3$ ), 5.01 and 5.18 (1 H each, br s, 17-H), and 5.44 (1 H, t,  $J$  3 Hz, 12-H);  $\delta_{\text{C}}$  170.5 (C-15), 168.8 (C=O of acetate), 139.7 (C-13), 103.6 (C-16), 74.1 (C-12), 57.8 (C-14), 56.1 (C-5), 52.3 (C-9), 50.25 ( $\text{OCH}_3$ ), 41.4 (C-3), 39.6 (C-1), 39.2 (C-7), 39.2 (C-8), 36.7 (C-10), 32.8 (C-18), 32.7 (C-4), 26.8 (C-11), 21.0 (C-19), 20.8 ( $\text{CH}_3$  of acetate), 18.1 (C-6), 17.9 (C-2), 15.4 (C-20), and 13.7 (C-17);  $m/z$  376 ( $M^+$ , 3%), 334 ( $M^+ - \text{CH}_2 = \text{C} = \text{O}$ , 9), 316 ( $M^+ - \text{AcOH}$ , 35), 301 (3), 257 (1), 205 (15), 191 (78), 178 (37), 173 (14), 163 (27), 159 (21), 145 (23), 137 (54), 133 (34), 121 (61), 112 (78), 109 (48), 105 (49), 95 (61), 91 (33), 81 (87), 69 (100), 55 (43), and 43 (46).

Compound (**21**) (680 mg, 1.79 mmol) dissolved in anhydrous dichloromethane (15 ml), at  $-78$  °C, was treated with an ozonized oxygen stream until all the starting material had disappeared. Dissolved unchanged ozone was removed with a slow nitrogen stream, and the ozonides were reduced during 15 min with trimethyl phosphite. The solvent was evaporated off, and the residual oil chromatographed, yielding the *oxo ester* (**22**) (530 mg, 1.40 mmol; 78%), m.p. 104.5–106 °C;  $\nu_{\max}$  (KBr) 2 960–2 880, 1 770, 1 740, 1 660, 1 620, 1 460, 1 370, 1 240, and 1 160  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.82 (3 H, s), 0.88 (6 H, s), 1.16 (3 H, s, 17-Me), 2.11 + 2.14 (3 H, s, acetate), 3.60 + 12.28 (1 H, s), 3.68 + 3.78 (3 H, s,  $\text{OCH}_3$ ), and 5.08 + 5.40 (1 H, t,  $J$  3 Hz, 12-H);  $\delta_{\text{C}}$  199.9 (C-13), 168.9 (C=O of acetate), 167.4 (C-15), 75.2 (C-12), 65.7 (C-14), 56.2 (C-5), 52.1 (C-9), 51.24 ( $\text{OCH}_3$ ), 43.4 (C-3), 41.6 (C-7), 40.3 (C-1), 39.7 (C-8), 37.2 (C-10), 33.1 (C-18), 32.9 (C-4), 27.8 (C-11), 21.1 (C-19), 20.7 ( $\text{CH}_3$  or acetate), 18.2 (C-6), 18.0 (C-2), 15.7 (C-10), and 15.0 (C-17) [enol form: 172.0 (C-13), 165.3 (C-15), 114.2 (C-14), 69.0 (C-12), and 24.0 (C-11)];  $m/z$  378 ( $M^+$ , 0%), 346 ( $M^+ - \text{MeOH}$ , 10%), 336 (10), 318 (4), 304 (26), 286 (10), 271 (20), 205 (9), 190 (100), 174 (26), 167 (17), 162 (14), 147 (18), 132 (24), 121 (33), 109 (41), 101 (15), 95 (66), 81 (63), 69 (77), 55 (36), and 43 (47).

To a solution (10 ml) of (**22**) (400 mg, 1.06 mmol) in dichloromethane, boron trifluoride-ether (0.1 ml) and ethane-1,2-dithiol (0.8 ml) were added. The mixture was left overnight at room temperature, then treated with ether (10 ml) and an excess of cold aqueous 10% sodium hydroxide, and extracted with ether (5 × 15 ml). The organic extract was washed, dried, and evaporated. The solid residue, after chromatography, gave the *dithioacetal* (**25**) (388 mg, 0.8 mmol; 75%) as a white solid, m.p.

140.5–142 °C;  $\nu_{\max}$  (KBr) 2 920, 2 860, 1 735, 1 450, 1 375, and 1 170  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.80 (3 H, s), 0.83 (6 H, s), 1.08 (3 H, s, 17- $\text{H}_3$ ), 2.33–3.53 (11 H, m), and 3.66 (3 H, s,  $\text{OCH}_3$ );  $\delta_{\text{C}}$  171.8 (C-15), 75.1 (C-13), 65.7 (C-14), 58.0 (C-12), 57.7 (C-9), 56.0 (C-5), 50.8 ( $\text{OCH}_3$ ), 41.6 (C-3), 40.9 (C-7), 40.5 (C-1), 40.0 (thioacetal), 39.8 (thioacetal), 39.2 (C-8), 38.7 (thioether), 38.7 (thioether), 37.22 (C-10), 33.1 (C-18), 33.02 (C-4), 24.5 (C-11), 21.2 (C-19), 18.2 (C-6), 18.1 (C-2), 16.4 (C-20), and 14.7 (C-17);  $m/z$  488 ( $M^+$ , 8%), 460 (10), 427 (8), 400 (4), 367 (7), 335 (6), 308 (7), 229 (4), 215 (3), 191 (9), 177 (9), 171 (24), 159 (6), 145 (9), 137 (21), 131 (100), 123 (14), 105 (28), 95 (23), 91 (13), 81 (23), 69 (26), 55 (14), and 41 (9).

A solution of the dithioacetal (**25**) (380 mg, 0.78 mmol) in absolute ethanol (30 ml) was stirred under reflux overnight in the presence of Raney nickel (*ca.* 4 g). The mixture was filtered through Celite, and the catalyst washed three times with hot ethanol; the combined filtrates were evaporated to give a colourless low-melting solid which after chromatography yielded the *ester* (**27**) (213 mg, 0.69 mmol; 89%). Crystallization from methanol gave white crystals, m.p. 85.5–87 °C;  $\nu_{\max}$  (KBr) 2 900, 2 840, 1 730 (ester), 1 445, 1 390, 1 365, 1 265, 1 210, 1 165, and 985  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.82 (3 H, s), 0.84 (3 H, s), 0.86 (3 H, s), 1.02 (3 H, s), and 3.62 (3 H, s,  $\text{OCH}_3$ );  $\delta_{\text{C}}$  174.8 (C-15), 59.2 (C-14), 57.3 (C-9), 56.5 (C-5), 50.6 ( $\text{OCH}_3$ ), 41.9 (C-3), 39.7 (C-1), 37.5 (C-8), 37.4 (C-10), 33.2 (C-18), 33.1 (C-4), 26.06 (C-13), 24.8 (C-12), 21.3 (C-19), 20.2 (C-11), 18.5 (C-6), 18.3 (C-2), 16.05 (C-20), and 15.02 (C-17);  $m/z$  306 ( $M^+$ , 13%), 291 (11), 250 (3), 191 (100), 177 (7), 163 (7), 149 (10), 123 (39), 109 (34), 95 (37), 87 (10), 81 (36), 67 (25), 55 (17), and 41 (8); (Found:  $M^+$ , 306.255 504. Calc. for  $\text{C}_{20}\text{H}_{34}\text{O}_2$ :  $M^+$ , 306.255 880).

(±)-13-*Norisocopalane-15-carboxylic Acid* (**9**).—To a stirred solution of lithium aluminium hydride (28 mg, 0.74 mmol) in ether, a solution of the ester (**27**) (200 mg, 0.65 mmol) in ether (5 ml) was added. The mixture was stirred for 30 min at 0 °C, then left overnight at room temperature, worked up with 0.25M sodium hydroxide (6.5 ml), and extracted with ether (2 × 15 ml); then addition of an excess of 20% hydrochloric acid, was followed by extraction with ether (2 × 20 ml), and the combined organic layers were washed with brine (2 × 10 ml), dried, and evaporated, affording the *alcohol* (**28**) (181 mg, 0.65 mmol; 100%), m.p. 118–120 °C (from MeOH);  $\nu_{\max}$  (KBr) 3 400–3 250, 2 920, 2 860, and 1 040  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.82 (3 H, s), 0.83 (6 H, s), 0.86 (3 H, s), and 3.56 (2 H, m, AB part of an ABX system);  $\delta_{\text{C}}$  63.3 (C-15), 59.8 (C-9), 56.4 (C-5), 54.3 (C-14), 42.0 (C-3), 41.0 (C-7), 39.9 (C-1), 37.5 (C-8), 37.1 (C-10), 33.2 (C-18), 33.1 (C-4), 26.9 (C-13), 25.4 (C-12), 21.4 (C-19), 20.6 (C-11), 18.6 (C-2), 18.6 (C-6), 16.3 (C-20), and 15.4 (C-17);  $m/z$  278 ( $M^+$ , 18%), 263 (16), 245 (2), 235 (1), 222 (3), 207 (2), 191 (100), 177 (6), 165 (7), 149 (13), 135 (15), 123 (27), 121 (19), 109 (45), 95 (50), 81 (29), 69 (24), 67 (20), 55 (2), and 41 (8).

To a stirred solution of the alcohol (**28**) (165 mg, 0.59 mmol) in dichloromethane (0.5 ml) and pyridine (1 ml), a solution of methanesulphonyl chloride (0.2 ml) in dichloromethane (2.5 ml) and pyridine (0.25 ml) was gradually added. After 12 h at room temperature, the mixture was poured into ice-water and stirred for an additional 3 h at room temperature. After addition of cold 20% hydrochloric acid (5 ml), the two-phase system was extracted with ether (4 × 15 ml). The extract was washed with aqueous 10% sodium hydrogen carbonate and brine, dried, and evaporated, yielding the *methanesulphonate* (**29**) (211 mg, 0.59 mmol; 100%), m.p. 118.5–120.5 °C (from MeOH);  $\nu_{\max}$  (KBr) 2 920, 2 860, 1 460, 1 410, 1 360 (mesylate), 1 180 (mesylate), 1 000, 960, and 860  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.80 (3 H, s), 0.82 (3 H, s), 0.85 (6 H, s), 2.97 (3 H, s,  $\text{SO}_2\text{CH}_3$ ), and 4.12 (2 H, m, AB part of an ABX system,  $\text{CH}_2\text{-OMs}$ );  $\delta_{\text{C}}$  71.4 (C-15), 59.5 (C-9), 56.3 (C-5), 50.7 (C-14), 41.9 (C-3), 40.9 (C-7), 39.9 (C-1), 37.5 (C-8), 37.5 (C-10), 37.1 (mesylate), 33.2 (C-4), 33.2 (C-18), 26.4 (C-13), 25.2 (C-12),

21.3 (C-19), 20.4 (C-11), 18.5 (C-6), 18.4 (C-2), 16.2 (C-20), and 15.4 (C-17);  $m/z$  356 ( $M^+$ , 5%), 341 (8), 245 (9), 191 (100), 177 (4), 163 (11), 149 (18), 137 (18), 136 (18), 123 (29), 121 (26), 109 (43), 95 (57), 81 (56), 69 (34), 67 (34), 55 (22), and 41 (11).

Sodium cyanide (100 mg, 2.04 mmol) was added to a solution of the methanesulphonate (**29**) (100 mg, 0.28 mmol) in dimethyl sulphoxide (2 ml). The mixture was heated at 90 °C overnight, with gentle stirring, then water (10 ml) was added. Extraction with ether (5 × 15 ml) followed by washing, drying, and evaporation of the extract, afforded a solid which was purified by sublimation at 6–10 mmHg and 60–80 °C, yielding the nitrile (**30**) (74 mg, 0.26 mmol; 92%), m.p. 124–125 °C;  $\nu_{\max}$  (KBr) 2 940, 2 860, 2 240 (nitrile), 1 460, and 1 390  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.80 (6 H, s), 0.82 (3 H, s), 0.85 (3 H, s), and 2.47 (2 H, m,  $\text{CH}_2\text{CN}$ );  $\delta_{\text{C}}$  120.3 (CN), 59.6 (C-9), 56.3 (C-5), 48.6 (C-14), 41.9 (C-3), 40.7 (C-7), 39.9 (C-1), 37.5 (C-8), 37.4 (C-10), 33.2 (C-4), 33.2 (C-18), 27.7 (C-13), 26.6 (C-12), 21.4 (C-19), 20.3 (C-11), 18.5 (C-6), 18.4 (C-2), 17.9 (C-15), 16.2 (C-20), and 14.0 (C-17);  $m/z$  287 ( $M^+$ , 12%), 272 (26), 191 (100), 174 (19), 137 (20), 123 (51), 109 (40), 95 (71), 81 (61), 67 (50), 55 (32), and 41 (21).

A solution of potassium hydroxide (1.5 g) and the nitrile (**30**) (60 mg, 0.21 mmol) in diethylene glycol (8 ml), was heated for 36 h at 200 °C. After cooling, water (24 ml) was added, and the mixture was extracted with ether (3 × 20 ml). The aqueous phase was acidified by dropwise addition of 12M hydrochloric acid, and extracted again with ether (3 × 25 ml). The combined extracts of the acidic fraction were washed with brine (25 ml), dried and evaporated, yielding the acid (**9**) (43 mg, 0.14 mmol; 68%), m.p. 185.5–187.5 °C (from MeOH);  $\nu_{\max}$  3 400–2 500 (carboxylic acid), 2 960, 2 860, and 1 710  $\text{cm}^{-1}$ ;  $m/z$  306 ( $M^+$ , 22%), 291 (15), 250 (9), 235 (3), 221 (3), 191 (100), 182 (5), 163 (5), 149 (5), 137 (12), 123 (22), 109 (23), 107 (9), 95 (25), 81 (16), 69 (12), 55 (4), and 43 (2) (Found:  $M^+$ , 306.255 196. Calc. for  $\text{C}_{20}\text{H}_{34}\text{O}_2$ :  $M^+$ , 306.255 880).

(±)-Methyl 13-Norisocopalane-15-carboxylate (**10**).—To a solution of the acid (**9**) (28 mg, 0.092 mmol) in cold ether (15 ml), an excess of ethereal diazomethane was added. The mixture was stirred for 1 h, then the unchanged diazomethane was destroyed with glacial acetic acid, and the solvent was removed. The residue was purified by sublimation, affording the ester (**10**) (29 mg, 0.09 mmol; 100%), m.p. 45–47 °C;  $\nu_{\max}$  2 960, 2 860, 1 735, 1 445, 1 385, 1 170, and 980  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.79 (9 H, s), 0.84 (3 H, s), 2.21 (2 H, m, AB part of an ABX system, 15-H), and 3.64 (3 H, s,  $\text{OCH}_3$ );  $\delta_{\text{C}}$  174.7 ( $\text{CO}_2\text{Me}$ ), 59.7 (C-9), 56.4 (C-5), 51.3 ( $\text{OCH}_3$ ), 48.3 (C-14), 42.0 (C-3), 40.5 (C-7), 39.9 (C-1), 37.4 (C-10), 37.4 (C-8), 34.9 (C-15), 33.5 (C-4), 33.5 (C-18), 28.2 (C-13), 26.9 (C-12), 21.4 (C-19), 20.5 (C-11), 18.6 (C-6), 18.5 (C-2), 16.2 (C-20), and 14.5 (C-17);  $m/z$  320 ( $M^+$ , 19%), 305 (25), 264 (7), 196 (7), 191 (100), 177 (12), 135 (16), 123 (32), 109 (38), 95 (42), 87 (21), 81 (37), 74 (40), 69 (32), and 55 (29).

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