Necic Acid Synthons. Part 1. Total Synthesis of Integerrinecic Acid

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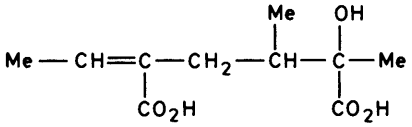
The synthesis of racemic integerrinecic acid from ethyl acrylate is described. Overall, five steps are involved. A key synthon in the synthesis, ethyl (2*Z*)-2-bromomethylbut-2-enoate, can undergo either allylic substitution or substitution with rearrangement, and opens the way for a ' general ' synthesis to a range of necic acids.

THE C_{10} necic acids are all derivatives of hexane-2,5-dioic acid and constitute the acidic portion of pyrrolizidine alkaloids. These alkaloids are widespread in Nature, and frequently occur as macrocyclic dilactones. Examples of commonly occurring necic acids are integerrinecic acid (1), retronecic acid (2), isolinecic acid (3), seneciphyllic acid (4), sceleranecic acid (5), and senecivernic acid (6). Many of the alkaloids are hepatotoxic and even nowadays are responsible for considerable stock losses.



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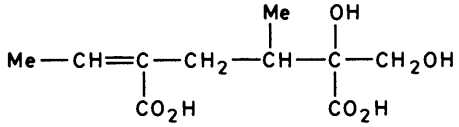

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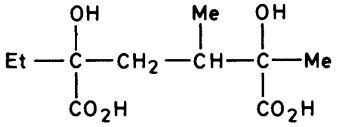

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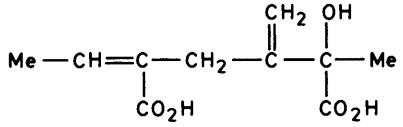

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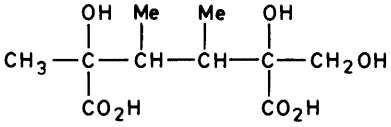

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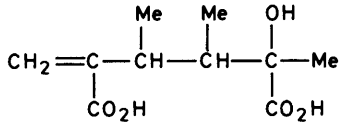

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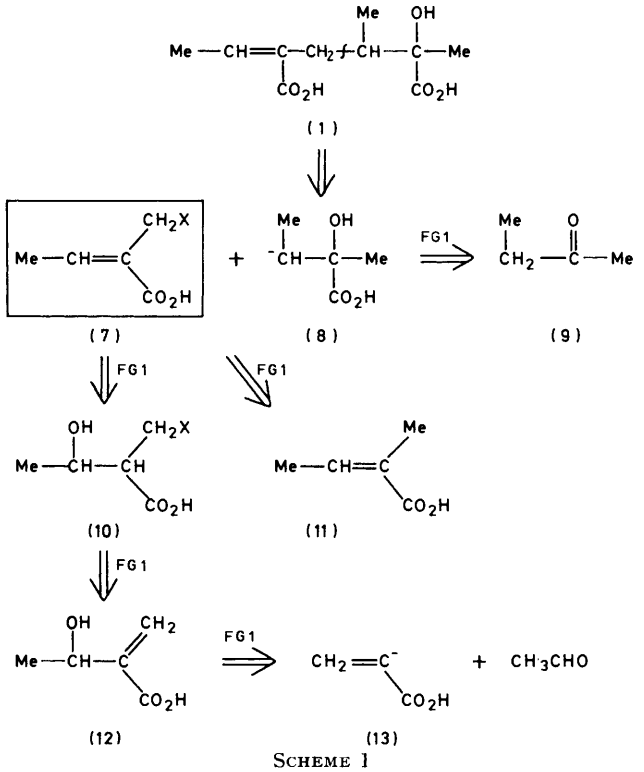
All the acids listed possess an α-hydroxy carboxylic acid group at C-5, four have a methyl substituent at C-4 and four contain an α,β-unsaturated system. In view of this it seemed of interest to us to devise a ' general ' method of synthesis in which a selected synthon could act as precursor for several of the necic acids. This seemed appropriate since integerrinecic acid,[1-5] seneciphyllic acid,[6,7] and senecivernic acid [8] are the only ones to have been synthesized to date. The procedures employed have generally been laborious with only moderate yields of the end product.

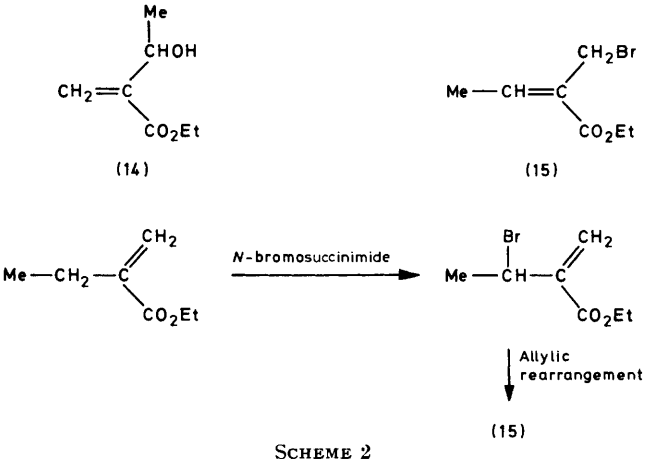
Using the classical retrosynthetic approach and employing intergerrinecic acid (1) as the target molecule, the synthons in Scheme 1 are obtained readily. The disconnection of the target molecule provides two possible routes to the important precursor (7). It can be obtained from tiglic acid (11) by allylic bromination or from a condensation between ethanal and the vinyl anion (13) of acrylic acid. While the tiglic acid route at first sight appears to be an attractive one, it has problems associated with it. Early workers [9-11] claimed that Wohl-Ziegler bromination of tiglic acid (11) gave only the β-bromotiglate but Dreiding and his co-workers [12,13] have subsequently shown that the β-bromotiglate was accompanied by a high proportion of the γ-bromo-derivative and that it was very difficult to separate the two isomers. We were able to confirm the findings of Dreiding and co-workers [13] so that the alternative route to the precursor (7) was explored. Among the methods investigated was that of Depezay and Le Merrer [14] (aldol condensation) and Goldberg and Dreiding [15] (a seven-step procedure starting with the ortho-ester of propanoic acid). Superior to either of these, however, was a method described in the patent literature [16] for the synthesis of the β-hydroxy-acid (12) and its subsequent conversion into the key synthon (7). In this synthesis ethyl acrylate condenses with ethanal in the presence of DABCO (1,4-diazabicyclo-[2,2,2]octane) to give an overall 94% yield of the β-hydroxy-ester (14). In our synthesis of integerrinecic acid (1) the hydroxy-ester (14) was converted into the allylic bromo-ester (15) in high yield using either th

N-bromosuccinimide–dimethyl sulphide procedure devised by Corey *et al.*[17] (and subsequently modified by Depezay and Le Merrer [14] and by Goldberg and Dreiding [15]) or the hydrobromic acid–sulphuric acid procedure.[18]



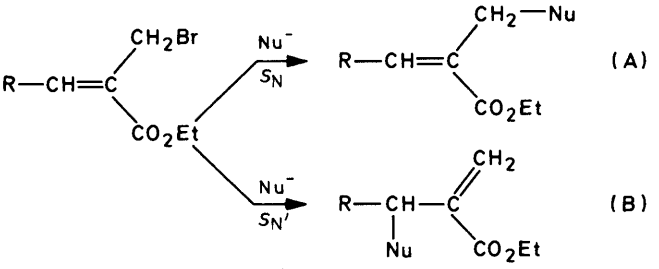
SCHEME 1

In the first total synthesis of integerrinecic acid (1) by Culvenor and Geissman [1] the acetyl derivative of the β-hydroxy-ester (14) was employed as an intermediate but its preparation from 3-acetoxybut-1-yne is laborious and several steps are involved. Pastewka *et al.*,[5] in their very recent publication, have used the β-bromo-ester (15) for conversion into integerrinecic acid. These authors obtain the ester *via* the series of reactions shown in Scheme 2. While the final allylic rearrangement



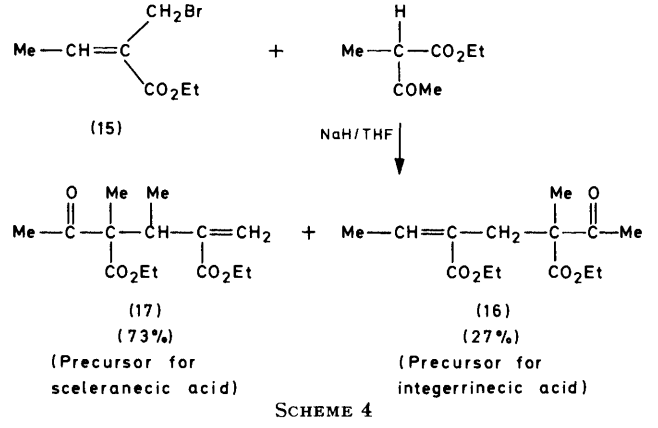
SCHEME 2

affords a good yield of the desired ester (15) the preliminary steps leading up to the starting material are in low yield. It is pertinent to point out that in neither of these two syntheses, which parallel ours in many aspects, do the authors discuss the scope of the synthons (14) and (15) as possible precursors for a ' general ' synthesis of necic acids. The β-bromo-ester (15) contains the labile



SCHEME 3

carbonyl allyl system and as such it can undergo nucleophilic substitution at the allylic position (S_N) or nucleophilic attack can occur at C-3 followed by concomitant rearrangement (S_N') with the loss of bromide anion (Scheme 3). The two products (A) and (B) constitute the ' left hand ' side and the ' right hand ' side of the necic acid molecule, respectively. By suitable manipulation of the reaction conditions and by judicious choice of the attacking nucleophile [19] it now becomes possible to postulate the synthesis of a wide range of necic acids. We



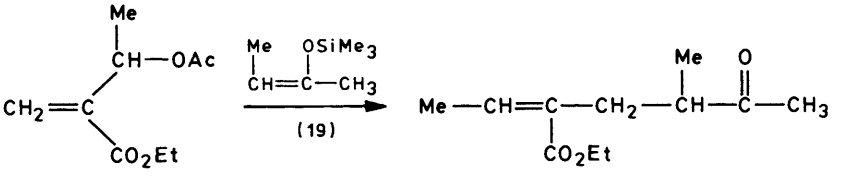
SCHEME 4

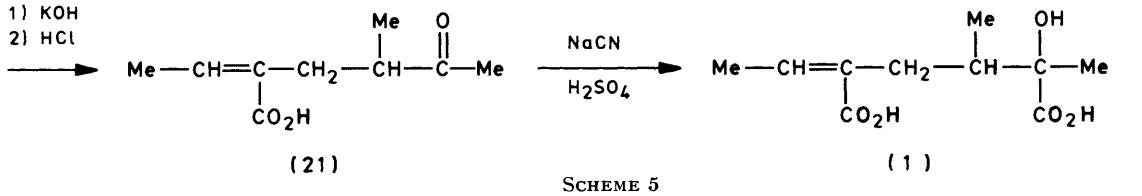
have also found [19] that variation of the substituent R (Scheme 3), while offering convenient routes to unnatural necic acids, also produces interesting trends in the regioselectivity of the nucleophilic displacements.

When ethyl 2-methyl-3-oxobutanoate (2-methyl derivative of acetoacetic ester) is used as nucleophile to react with the β-bromo-ester (15), two products (16) and (17), as outlined above, were obtained (Scheme 4). The intermediate (16) which can, after suitable interconversion, lead to integerrinecic acid was present as the minor component (27%). The major component (17), which is a precursor for the elusive sceleranecic acid, was readily separated from (16) by preparative gas chromatography.

Since it was our intention to obtain integerrinecic acid

in high yield the other synthon (10) in Scheme 1 was investigated at this stage as a possible precursor. Following the earlier lead given by Culvenor and Geissman [1] it was acetylated to give the acetate (18). This reacted smoothly with the silyl enol ether (19) in the presence of titanium tetrachloride at −78 °C to give the keto-ester (20) in 63% yield. Mild base hydrolysis afforded the keto-acid (21) in good (68%) yield. This route to compound (21) affords higher yields and is one step shorter than Culvenor and Geissman's method [1] in which the acetate





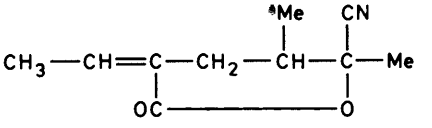
SCHEME 5

(18) is treated with ethyl 2-methyl-3-oxobutanoate. The pathway described by us avoids the use of harsh hydrolysis and dealkoxycarbonylation to arrive at the keto-acid (21). This keto-acid represents the ' backbone ' of integerrinecic acid (1) and its transformation to the cyanohydrin and subsequent hydrolysis to the target molecule (1) was achieved using standard procedures (Scheme 5). Our synthesis is shorter than any of the published routes involving five steps only. Yields of the two initial steps are in excess of 90% while the last three, though at acceptable levels, merit further investigation.

There are several aspects of the synthesis which require further discussion. These are as follows.

(*i*) *The aldol condensation using DABCO as base.* Two possible mechanisms can operate for this reaction. The DABCO can act either as a nucleophile in which case attack occurs at C-3 of the acrylate system or it can act as base leading to formation of a vinyl carbanion. We favour the first mechanism and experiments are underway to clarify this situation. From observations of Feit *et al.*[20] on the reaction between methyl acrylate and benzophenone in the presence of the lithium salt of 2,2,6,6-tetramethylpiperidine no unambiguous conclusion can be drawn but the evidence is slightly in favour of the first mechanism.

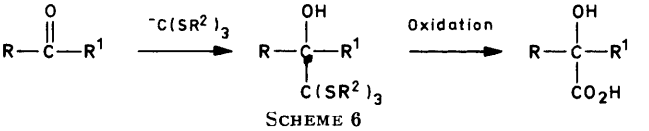
(*ii*) *The cyanohydrin reaction.* All published syntheses of necic acids proceed *via* this route to convert the appropriate ketone into an α-hydroxycarboxylic acid. Invariably the yields are only moderate. Pastewka *et al.*[5] quote a 60% conversion and in our hands it was 78%. While there is no great difficulty in obtaining the cyanohydrin intermediate, the problems usually arise during acid hydrolysis of the latter when loss of hydrogen cyanide leads to isolation of starting material. In our hands the keto-ester (20), after ready conversion into the cyanohydrin, afforded the starting material almost quantitatively on acid hydrolysis. This result was not changed by ' protecting ' the hydroxy-group (in the cyanohydrin) as the trimethylsilyl ether [21–23] prior to acid hydrolysis. It was then reasoned that it might be advantageous to utilize the keto-acid (21), rather than the corresponding ester (20) since this would encourage formation of the stable δ-lactone (22) which could be isolated, ring-opened under base conditions, and converted into the required acid (1). This modification proved to be successful. On the available evidence it is not possible to



(22)

speculate on the relative proportions of the diastereoisomers formed but it is highly unlikely that only the integerrinecic isomer was obtained.

An alternative procedure for the introduction of an α-hydroxy carboxylic function from a ketone relies on an oxidative rather than a hydrolytic pathway and this was



SCHEME 6

investigated by us. Seebach *et al.*[24] and also others,[25,26] have reported conversion of the ketone into an hydroxy-orthothioformate followed by oxidative cleavage [27] to the carboxyl function (Scheme 6). Our attempted reaction of the keto-ester (20) with both tris(phenylthio)methane and tris(ethylthio)methane was unsuccessful and gave

back only starting material. This inability of the orthothioformates to react with the keto-ester (20) is presumed to be due to steric hindrance but this type of oxidative conversion requires further investigation.

(*iii*) *Stereochemistry of the integerrinecic acid*. Our allocation of an *E*-(*trans*-)configuration to the title acid is based on spectroscopic evidence. The downfield position of the vinylic proton (δ 6.88) in the ^{1}H n.m.r spectrum has been used previously [28] to designate the *E*-configuration. This result was also confirmed by the ^{13}C n.m.r. spectrum of (1). We have found previously [29] that the chemical shift of the vinylic methylene group reflects the stereochemistry around the double bond. If this methylene group resonates at *ca.* δ 28, the configuration is likely to be *E*, while a peak at *ca.* δ 38 indicates *Z* geometry. In the title compound the methylene group in question resonates at δ 28.98.

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian T60 or a Varian FT80A instrument and deuteriochloroform was used as the solvent unless otherwise stated.

Ethyl 3-*Hydroxy*-2-*methylenebutanoate* (14).—Ethanal (88 g), ethyl acrylate (130 g), and DABCO (7.28 g) were stirred together in a sealed flask for 7 d at 25 °C. The solution was then washed successively with 6M-hydrochloric acid, 2M-aqueous sodium hydroxide, and saturated aqueous sodium chloride. Distillation of the organic layer yielded the desired product (176.5 g, 94%), b.p. 89—91 °C at 17 mmHg (lit.,[15] b.p. 70 °C/9 mmHg); *m/z* 129 (M^+ − 15, 57%), 101 (70), 99 (47), and 83 (100); δ 1.33 (3 H, t, CH_2CH_3), 1.40 (3 H, d, $CHCH_3$), 3.80 (1 H, s, OH), 4.33 (2 H, q, CH_2CH_3), 4.72 (1 H, q, $CHCH_3$), and 5.93 and 6.30 (2 H, d, *J* 0.5 Hz, $C=CH_2$).

Ethyl (2Z)-2-*Bromomethylbut*-2-*enoate* (15).—A solution of dimethyl sulphide (17.67 g) in dichloromethane (50 ml) was added dropwise to a solution of *N*-bromosuccinimide (49.4 g) in dichloromethane (100 ml) at 0 °C under a nitrogen atmosphere. A yellow precipitate formed after a few minutes. Ethyl 3-hydroxy-2-methylenebutanoate (20 g) in dichloromethane (50 ml) was added slowly and the solution was stirred at 25 °C for 6 h. The solution was diluted with pentane (200 ml) and then poured into a cold, saturated aqueous sodium chloride (200 ml). The aqueous phase was extracted with pentane and the combined organic phases were dried ($MgSO_4$) and distilled (16.7 g, 58%), b.p. 70—75 °C/4 mmHg (lit.,[15] b.p. 40 °C/0.1 mmHg); *m/z* 208 (M^+, 6%), 206 (M^+, 6), 163 (17), 161 (17), 127 (100), 99 (51), and 81 (45); δ 1.33 (3 H, t, CH_2CH_3), 1.90 (3 H, d, $CHCH_3$), 4.23 (2 H, s, CH_2Br), 4.25 (2 H, q, CH_2CH_3), and 7.00 (1 H, q, *J* 3.5 Hz, $CHCH_3$).

Acid derivative, m.p. 111 °C (Found: C, 33.6; H, 4.15. Calc. for $C_5H_7BrO_2$: C, 33.55; H, 3.94%).

Ethyl (2Z)-2-*Bromomethylbut*-2-*enoate* (15): *Alternative Procedure*.—Ethyl 3-hydroxy-2-methylenebutanoate (50 g) was stirred for 12 h at 25 °C with hydrobromic acid (48% 160 g) and concentrated sulphuric acid (10 ml). The solution was extracted with diethyl ether, dried, and distilled (52.4 g, 73%).

Ethyl 3-*Acetoxy*-2-*methylenebutanoate* (18).—One drop of concentrated sulphuric acid was added to a solution of ethyl 3-hydroxy-2-methylenebutanoate (60 g) and acetic anhydride (75 g). The exothermic reaction was cooled in an ice-bath, left for 30 min, and then poured into water (200 ml) and extracted with diethyl ether. The combined ether layers were dried (Na_2SO_4) and then distilled (72.3 g, 93%), b.p. 65—69 °C/1 mmHg (lit.,[1] b.p. 56 °C/0.5 mmHg) (Found: C, 58.05; H, 7.6. Calc. for $C_9H_{14}O_4$: C, 58.05; H, 7.57%); *m/z* 143 (M^+ − Ac, 39%), 141 (16), 115 (11), and 97 (42); δ 1.32 (3 H, t, CH_2CH_3), 1.42 (3 H, d, $CHCH_3$), 2.10 (3 H, s, $COCH_3$), 4.27 (2 H, q, CH_2CH_3), 5.77 (1 H, q, $CHCH_3$), and 5.82 and 6.32 (2 H, d, $C=CH_2$).

Diethyl 5-*Methyl*-6-*oxohept*-2-*ene*-3,5-*dicarboxylate* (16) *and Diethyl* 3,4-*Dimethyl*-5-*oxohex*-1-*ene*-2,4-*dicarboxylate* (17).—To a stirred suspension of sodium hydride (80% in oil; 0.83 g) in dry tetrahydrofuran (50 ml) was added a solution of ethyl 2-methyl-3-oxobutanoate (4 g) also in dry tetrahydrofuran (50 ml). After 1 h a solution of ethyl 2-bromomethylbut-2-enoate (15) in the same solvent (50 ml) was added and the mixture was stirred for 2 h. The reaction was quenched with water (200 ml) and the solution extracted with ether. The combined ether extracts, after being dried (Na_2SO_4), were concentrated under reduced pressure to give an oil (6.93 g, 93% of mixture). Separation by preparative gas chromatography (15% SE-30, Chromosorb W 42-60) afforded 73% of the *diethyl ester* (17) and 27% of the *diethyl ester* (16) [Found: for the ester (17): C, 61.95; H, 8.2. $C_{14}H_{22}O_5$ requires C, 62.20; H, 8.20%); *m/z* 228 (11%), 182 (22), 154 (60), 110 (16), and 98 (18); δ 1.23 (6 H, t, 2 × CH_2CH_3), 1.27 (3 H, s, CCH_3), 1.30 (3 H, d, $CHCH_3$), 2.20 (3 H, s, $COCH_3$), 3.80 (1 H, q, $CHCH_3$), 4.20 (4 H, q, 2 × CH_2CH_3), and 5.57 and 6.27 (2 H, dd *J* 0.5 Hz, $C=CH_2$). The dibromide of this compound had M^+ 432 [Found for the ester (16): C, 62.15; H, 8.3. $C_{14}H_{22}O_5$ requires C, 62.20; H, 8.20%]; *m/z* 270 (M^+, 3%), 228 (32), 225 (29), 197 (4), 181 (38), 154 (89), and 125 (100); δ 1.23 (6 H, t, 2 × CH_2CH_3), 1.27 (3 H, s, CCH_3), 1.80 (3 H, d *J* 3.9 H_3, $C=CHCH_3$), 2.17 (3 H, s, $COCH_3$), 2.98 (2 H, s, CCH_2C), 4.13 (2 H, q, CH_2CH_3), 4.18 (2 H, q, CH_2CH_3), and 6.98 (1 H, q, *J* 3.5 Hz $C=CHCH_3$).

Ethyl (2Z)-2-*Ethylidene*-4-*methyl*-5-*oxohexanoate* (20).—The 2-trimethylsilyloxybut-2-ene (19) used in this reaction was prepared by a method similar to that employed by House *et al.*[30] To a solution of chlorotrimethylsilane (32.6 g) and triethylamine (60.6 g) in dry dimethylformanide (100 ml) was added butan-2-one (18 g). The resulting mixture was heated under reflux for 16 h during which time triethylamine hydrochloride was precipitated. The mixture was cooled, diluted with pentane (200 ml), and washed with cold, aqueous sodium hydrogencarbonate. From the pentane extract the desired silyl ether (29.9 g, 83%) was distilled, b.p. 114—116 °C. A stirred solution of titanium tetrachloride (20.76 g) in dichloromethane (20 ml) was cooled to −78 °C under a nitrogen atmosphere. To this were added successively ethyl 3-acetoxy-2-methylenebutanoate (18) (18 g) in dichloromethane (50 ml) and 2-trimethylsilyloxybut-2-ene (14 g) in dichloromethane (50 ml). After being stirred for 3 h at −78 °C, the reaction was quenched with saturated aqueous ammonium chloride at −60 °C. The organic layer was separated and the aqueous layer extracted with diethyl ether and dried (K_2CO_3). Distillation under reduced pressure of the combined organic layers gave the desired product (12.05 g, 63%), b.p. 88 °C/4 mmHg; *m/z* 198 (M^+, 11%), 152 (43), 137 (27), 127 (21), and 109 (43); δ 1.03 (3 H, d, $CHCH_3$), 1.30 (3 H, t, CH_2CH_3), 1.82 (3 H, d, $CH=CHCH_3$), 2.15 (3 H, s, $COCH_3$), 2.30 (2 H, d, CH_2CH), 2.62 (1 H, m,

CH_2CHCH_3), 4.20 (2 H, q, CH_2CH_3), and 6.93 (1 H, q J 3.5 Hz, $C=CHCH_3$).

(2E)-2-*Ethylidene*-4-*methyl*-5-*oxohexanoic Acid* (21).—Ethyl 2-ethylidene-4-methyl-5-oxohexanoate (5 g) was stirred with aqueous 1M-potassium hydroxide (25.3 ml) for 12 h at 25 °C. The solution was then acidified with 1M-hydrochloric acid and extracted with diethyl ether. Concentration of the extracts under reduced pressure gave a yellow oil (2.96 g, 69%) which slowly crystallized, m.p. 49—50 °C (from pentane) (lit.,[1] m.p. 49—51 °C). Alternatively, this acid was obtained from diethyl 5-methyl-6-oxohept-2-ene-3,5-dicarboxylate (16) [prepared in 93% yield from ethyl acetoacetate and compound (18)] by reacting it (15 g) with sodium iodide (16.79 g), methyl cyanide (100 ml) and trimethylchlorosilane (12.15 g) under a nitrogen atmosphere. The solution was heated at reflux temperature for 4 h, cooled, diluted with water (100 ml), and refluxed for a further 2 h. Extraction with ether gave a yellow oil which crystallized slowly from pentane (7.3 g, 78%), m.p. 50 °C (Found: C, 63.25; H, 8.2. Calc. for $C_9H_{14}O_3$: C, 63.51; H, 8.29%); m/z 170 (M^+, 7%), 152 (41), 137 (26), 109 (37), 81 (53), and 43 (100); δ 1.05 (3 H, d J 3.1 Hz, $CHCH_3$), 1.83 (3 H, d J 3.9 Hz, $C=CHCH_3$), 2.17 (3 H, s, $COCH_3$), 2.55 (1 H, m, CH_2CHCH_3), 2.60 (2 H, m, CH_2CH), and 7.03 (1 H, q J 3.5 Hz, $C=CHCH_3$); δ_C 14.91 (C-9), 15.77 (C-7), 28.75 (C-6), 28.98 (C-3), 45.97 (C-4), 130.19 (C-2), 142.46 (C-8), 172.94 (C-1), and 212.32 (C-5).

(2E)-6-*Hydroxy*-5-*methylhept*-2-*ene*-3,6-*dicarboxylic Acid* (1) (*Integerrinecic Acid*).—Sodium cyanide (0.54 g) was dissolved in water (3 ml) and 2-ethylidine-4-methyl-5-oxohexanoic acid (21) (1.87 g) was added. The stirred solution was cooled to 0 °C and 0.01M-sulphuric acid (1.08 g) was added slowly so that the temperature remained below 5 °C. Extraction with diethyl ether gave the cyanohydrin (1.69 g, 78.3%) which was shown to be pure by n.m.r. spectroscopy. δ 1.00 (3 H, d, $CHCH_3$), 1.60 (3 H, s, CCH_3), 1.87 (3 H, d, $C=CHCH_3$), 2.03—2.77 (3 H, m, CH_2CH), 5.43 (2 H, s, COOH, OH), and 7.10 (1 H, q, $C=CHCH_2$). On account of its instability, the cyanohydrin (2 g) was hydrolysed immediately to the corresponding acid by stirring it with concentrated hydrochloric acid (15 ml) for 12 h at 5 °C. The solution was then kept at steam-bath temperature for 7 h, cooled, and extracted with diethyl ether. The combined ether extracts were dried (sodium sulphate) and concentrated under reduced pressure to give a dark brown oil. This was dissolved in 1M aqueous sodium hydroxide (20 ml), extracted with chloroform, and the aqueous solution passed through a neutral cation exchange resin (Zeocarb 225). Concentration of the eluant under reduced pressure gave the crude acid which crystallized from ethyl acetate (1.17 g, 63%), m.p. 145—147 °C (lit.,[5] 146—149 °C) (Found: C, 55.45; H, 7.45. Calc. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46%); m/z 198 ($M^+ - H_2O$, 8%), 180 (11), 162 (12), 153 ($M^+ - H_2O - CO_2H$, 100), 134 (19), 125 (22), 109 (21), 107 (15), and 81 (60); δ (CD_3OD) 0.85 (3 H, d J 3.1 Hz, $CHCH_3$), 1.38 (3 H, s, CCH_3), 1.80 (3 H, d J 3.9 Hz, $C=CHCH_3$), 2.32 (3 H, m, $-CH_2CH$), and 6.88 (1 H, q J 3.3 Hz, $C=CHCH_3$). The compound proved to be identical in all respects (m.p., mass and n.m.r. spectrum) with an authentic sample of (+)-integerrinecic from *Senecio adnatus*.

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REFERENCES

[1] C. C. J. Culvenor and T. A. Geissman, *J. Am. Chem. Soc.*, 1961, **83**, 1647.
[2] N. K. Kochetkov, A. E. Vasil'ev, and S. N. Levchenko, *Zh. Obshch. Khim.*, 1964, **34**, 2202 (*Chem. Abstr.*, 1964, **61**, 9399d).
[3] J. D. Edwards, T. Hase, C. Hignite, and T. Matsumato, *J. Org. Chem.*, 1966, **31**, 2282.
[4] J. D. Edwards and T. Matsumato, *J. Org. Chem.*, 1967, **32**, 1837.
[5] U. Pastewka, H. Wiedenfeld, and E. Röder, *Arch. Pharm.*, 1980, **313**, 846.
[6] J. D. Edwards, T. Hase, and N. Ichikawa, *Chem. Commun.*, 1965, 364.
[7] J. D. Edwards, T. Hase, and N. Ichikawa, *J. Heterocycl. Chem.*, 1967, **4**, 487.
[8] U. Pastewka, H. Wiedenfeld, and E. Röder, *Arch. Pharm.*, 1980, **313**, 785.
[9] F. Korte and V. Behner, *Chem. Ber.*, 1956, **89**, 2675.
[10] H. H. Inhoffen, S. Bork, and B. Schwieter, *Liebig's Ann. Chem.*, 1953, **580**, 1.
[11] H. H. Inhoffen, V. Isler, G. van der Bey, G. Raspe, P. Zeller, and R. Ahrens, *Liebig's Ann. Chem.*, 1953, **580**, 7.
[12] A. Löffler, R. J. Pratt, H. P. Ruesch, and A. S. Dreiding, *Helv. Chim. Acta*, 1970, **53**, 383.
[13] L. K. Sydnes, L. Skattebol, C. B. Chapleo, D. G. Leppard, K. L Svanholt, and A. S. Dreiding, *Helv. Chim. Acta*, 1975, **58**, 2061.
[14] J.-C. Depezay and G. Le Merrer, *Tetrahedron Lett.*, 1974, 2751.
[15] V. Goldberg and A. S. Dreiding, *Helv. Chim. Acta*, 1976, **59**, 1904.
[16] A. B. Baylis and M. E. Hillman, German Patent 2155113 (May 1972) (*Chem. Abstr.*, 1972, **77**, 34174q).
[17] E. J. Corey, M. Uhno, B. B. Mitra, and P. A.Vatakencherry, *J. Am. Chem. Soc.*, 1964, **86**, 478.
[18] M. Kaeriyama, T. Sato, S. Hashimoto, M. Mizuno, M. Ando, and H. Yoneda, Japanese Patent, 7695016 (August 1976) (*Chem. Abstr.*, 1976, **85**, 176872e).
[19] Unpublished results.
[20] B. A. Feit, U. Melamed, R. R. Schmidt, and H. Speer, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1329.
[21] D. A. Evans, L. K. Truesdale, and G. L. Carroll, *J. Chem. Soc., Chem. Commun.*, 1973, 55.
[22] J. K. Rasmussen and S. M. Heilman, *Synthesis*, 1978, 219.
[23] D. A. Evans and L. K. Truesdale, *Tetrahedron Lett.*, 1973, 4929.
[24] D. Seebach, K-H. Geiss, A. K. Beck, B. Graf, and H. Daum, *Chem. Ber.*, 1972, **105**, 3280.
[25] A. Fröling and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1962, **81**, 1009.
[26] R. Engler, G. Gattow, and M. Draeger, *Z. Anorg. Allg. Chem.*, 1972, **390**, 64.
[27] V. D Dailey and R. L. Fuchs, *J. Org. Chem.*, 1980, **45**, 216.
[28] L. B. Bull, C. C. J. Culvenor, and A. T. Dick, 'The Pyrrolizidine Alkaloids,' North Holland Publishing Co., Amsterdam, 1968.
[29] S. E. Drewes, I. Antonowitz, P. T. Kaye, and P. C. Coleman, *J. Chem. Soc., Perkin Trans. 1*, 1981, 287.
[30] H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.