The chemistry of thujone. II.[1] Insect juvenile hormone analogues via acid dianion coupling. The β lactone route

JAMES P. KUTNEY, MICHAEL J. MCGRATH, ROBERT N. YOUNG, AND BRIAN R. WORTH
Department of Chemistry, University of British Columbia, 2075 Wesbrook Place, Vancouver, B.C., Canada V6T 1W5

Received May 25, 1979

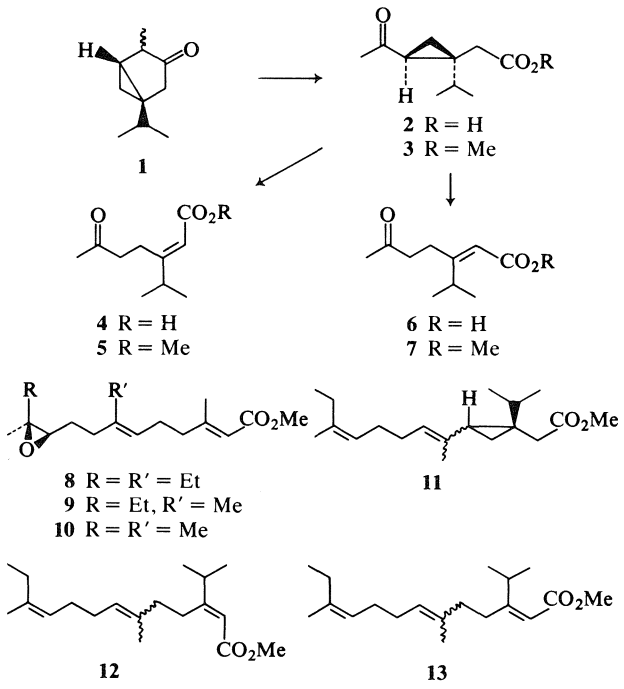
JAMES P. KUTNEY, MICHAEL J. MCGRATH, ROBERT N. YOUNG, and BRIAN R. WORTH. Can. J. Chem. **57**, 3145 (1979).

Several stereoselective syntheses of (*E*)-2-ethyl-6-methyl-5-octenoic acid (**17**) are described. The dianion of pure **17** was subsequently coupled with (*E*)-β-thujaketonic acid methyl ester (**5**), derived from thujone (**1**), to give the β-lactones **45** and **46** which were then epoxidized and pyrolyzed exemplifying a route to juvenile hormone analogues such as **51** and **54**.

JAMES P. KUTNEY, MICHAEL J. MCGRATH, ROBERT N. YOUNG et BRIAN R. WORTH. Can. J. Chem. **57**, 3145 (1979).

On décrit plusieurs synthèses stéréosélectives de l'acide (*E*)-éthyl-2 méthyl-6 octène-5 oïque. Le dianion pur de **17** couplé à l'ester méthylique de l'acide (*E*)-β-thujacétonique (**5**) provenant de la thujone (**1**) conduit aux β lactones **45** et **46**. Ces derniers sont alors transformés en époxyde qui, par pyrolyse, permettent d'accéder aux analogues **51** et **54** de l'hormone juvénile.
[Traduit par le journal]

The steam distillate from the slash (waste) of the western red cedar is an excellent source of the monoterpenoid ketone, thujone (**1**) (1, 2). In an effort to further exploit the ready availability and interesting functionality of **1**, its utility in a general route to a series of insect juvenile hormone (JH) analogues was investigated. Permanganate oxidation (2) of thujone[2] had provided α-thujaketonic acid (**2**) which could be ring opened, thermally to give (*E*)-β-thujaketonic acid (**4**), or via base catalysed cleavage of the ester (**3**) to give (*Z*)-β-thujaketonic acid methyl ester (**7**) (1). The gross structural similarities between the synthetic units, **3**, **5**, and **7** and the "right hand" portion of the juvenile hormones **I**, **II**, and **III** (**8**–**10**) pointed to a potential usage of thujone derived intermediates. In fact an earlier report (1) described the coupling of these keto-acids and esters with C8-units, via Wittig olefination, to give analogues such as **11**, **12**, and **13**. This method was, however, limited to the preparation of derivatives with a trisubstituted internal double bond, thus limiting the series of analogues available for biological screening. A further detriment to this route lay in the difficulty experienced in separating the *E*- and *Z*-isomers (at C6) formed during the coupling.



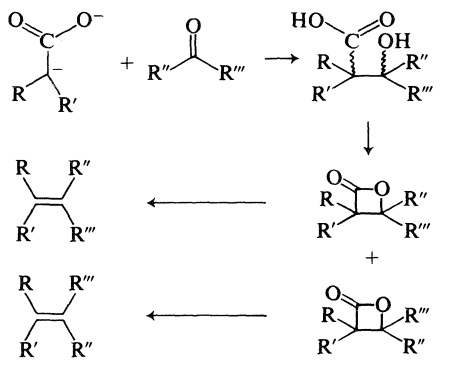
SCHEME 1

Thus, in order to circumvent these difficulties it was necessary to devise an alternative route which, ideally, would fulfill four important requirements: (*i*) the ability to generate tri- and tetrasubstituted internal unsaturations, (*ii*) a mode of coupling that would allow at least selective *trans*-isomer formation, (*iii*) facile separation of the isomeric alkenes, (*iv*) specific protection of the internal double bond so as to allow specific epoxidation at C10(11). Of the various methods available (3–10), that involving coupling between a carboxylic acid dianion and a ketone to give a β-hydroxy acid, generation of di-

[1]For Part I, see ref. 1.

[2]Although thujone exists in two epimeric forms at C4, oxidative cleavage to **2** destroys this chiral centre thus allowing crude thujone to be used for this work.

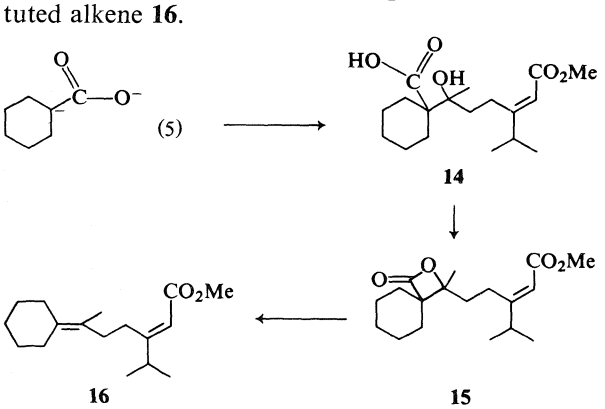
0008-4042/79/233145-10$01.00/0



SCHEME 2

astereomeric β-lactones, and subsequent thermal elimination of carbon dioxide (Scheme 2) seemed the most suitable (4, 11, 12).

To determine the suitability of the thujone-derived ketoesters for the proposed route, the dianion from cyclohexane carboxylic acid was reacted with (*E*)-β-thujaketonic acid methyl ester (**5**). The required adduct **14** was formed in 60% yield. Subsequent reaction with benzenesulphonyl chloride in pyridine provided the β-lactone **15** as evidenced by characteristic infrared absorption at 1810 cm^{-1}. Pyrolysis of **15** at 140°C gave a 68% yield of the expected tetrasubstituted alkene **16**.



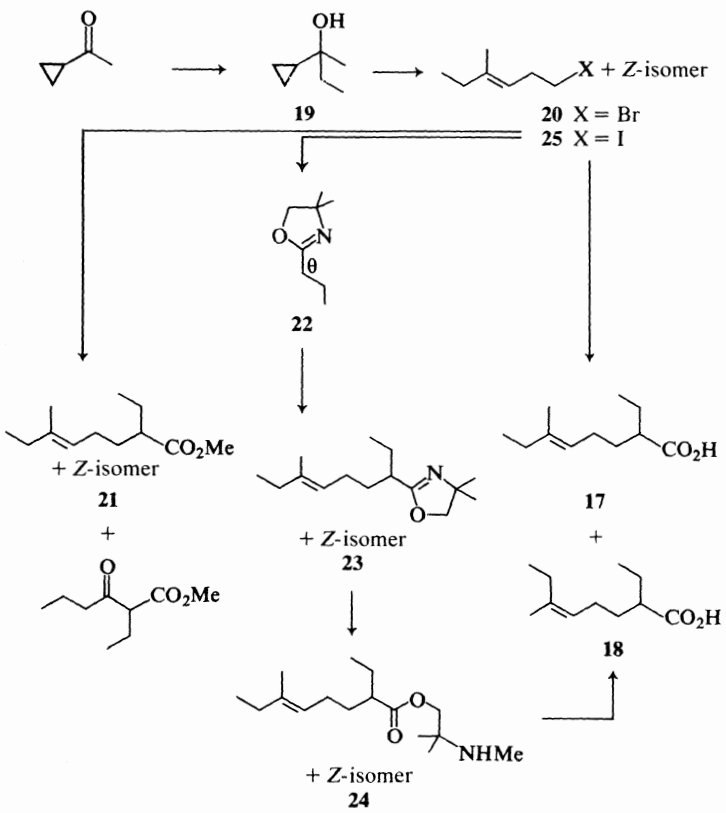
SCHEME 3

With the success of the model sequence, the preparation of prerequisite acid units representing the "left hand" portion of juvenile hormones **8**–**10** was necessary. Initially, the more troublesome targets **17** and **18**, related to the C18 cecropia juvenile hormones (**8** and **9**), were chosen since successful application of the proposed scheme with these units would effectively guarantee a route to the analogue related to **10**.

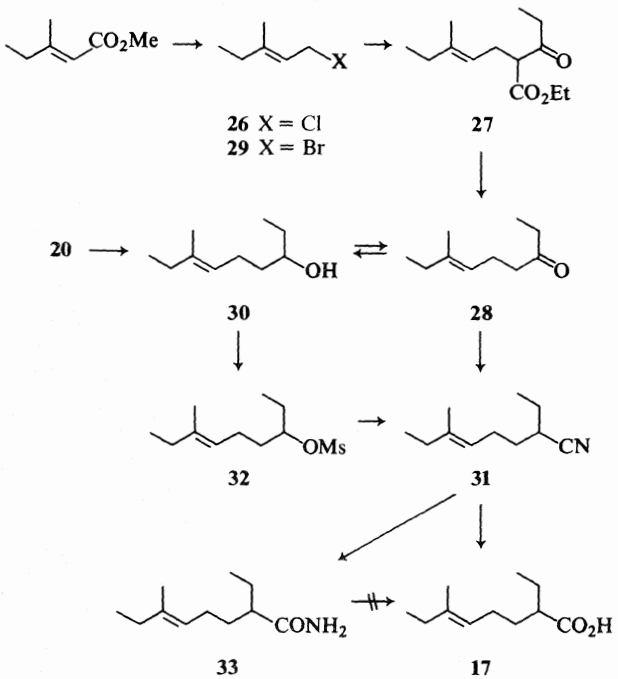
An efficient synthesis of a mixture of the *E*- and *Z*-octenoic acids **17** and **18** was available, based on the known cyclopropylcarbinol–homoallyl rearrangement (13–16), as shown in Scheme 4. Grignard reaction on methyl cyclopropyl ketone afforded the known carbinol **19** (13) which on reaction with magnesium bromide (17, 18) in ether gave a mixture of the *E*- and *Z*-homoallylic bromides **20**. Initially this mixture was used to alkylate (19) the α-anion of methylbutanoate giving only a low yield of the esters **21** admixed with the Claisen product (20), methyl-2-ethyl-3-oxohexanoate. Similar alkylation of the anion **22**, of the oxazoline (21, 22) formed by reaction between butanoic acid and 2-amino-2-methyl-1-propanol, gave only a 44% yield of the adducts **23**. Direct, acid catalysed hydrolysis of **23** was not successful; however, methylation using iodomethane and subsequent aqueous base catalysed hydrolysis gave the esters **24**. Reaction of **24** in aqueous ethanolic sodium hydroxide solution at 50°C did provide a route, albeit inefficient, to the required acids. Reaction of the dianion of butanoic acid (23) with the bromides **20** in a mixture of tetrahydrofuran (THF) and hexamethylphosphortriamide (HMPA) provided the *E*- and *Z*-acids **17** and **18** directly. Best results were obtained by analogous alkylation with the relatively unstable iodides **25**, formed by reaction of the mixture **20** with sodium iodide in acetone or more efficiently by ring opening of **19** with magnesium iodide in ether (17, 18). In this manner an 80% yield (from **19**) of the acids **17** and **18** was obtained. Separation of the isomeric acids **17** and **18** was not possible by glc or by tlc methods. Accurate determination of the ratio of these products was however possible from areas of the resonances due to C5 in the ^{13}Cmr spectrum (24). In this manner, the composition was determined as 80% *E*- (**17**), 20% *Z*- (**18**).

Although this route provided a fast and efficient means of obtaining the octenoic acids for developing the efficiency of subsequent reactions, in order to ensure the integrity of juvenile hormone analogues for biological screening a stereospecific route to **17** or **18** was necessary.

Initially, the synthesis outlined in Scheme 5 was investigated. Horner reaction between 2-butanone and the sodium salt of trimethylphosphonoacetate afforded *E*- and *Z*-methyl-3-methyl-2-pentenoates which were separated by spinning band distillation as described earlier (1, 25). The major, *E*-isomer was elaborated by standard means to the pure *E*-allylic chloride **26** (1). Alkylation of ethyl-3-oxopentanoate (26) with **26** in 1,2-dimethoxyethane (DME) gave pure *E*-β-ketoester **27**. For each intermediate in this route (Scheme 5) the respective *E*- and *Z*-isomers were not separable by either tlc or conventional glc systems. Therefore *E*-, *Z*- mixtures of the intermediates up to and including **27** were initially prepared as described above from a mixture (ca. 2:1) of *E*- and *Z*-methyl-3-methyl-2-pentenoates. In each case the differences in chemical shift for the vinylic methyl signals in 270 MHz ^{1}Hmr proved satisfactory



SCHEME 4

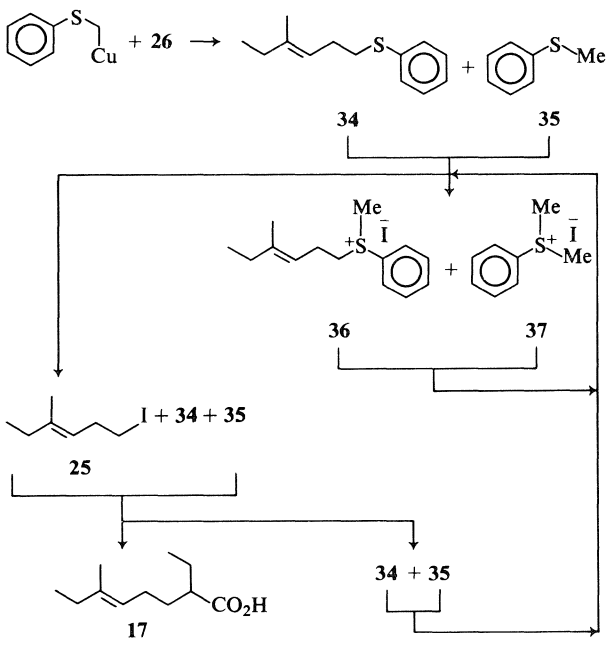


SCHEME 5

for the determination of isomer ratios. These chemical shift values were then used to determine the integrity of subsequent purity of compounds within the *E* series. Examination of **27** (derived from pure *E*-methyl-3-methyl-2-pentenoate) by 270 MHz ^{1}Hmr spectroscopy did not show detectable *Z*-isomer (1). An *E*-, *Z*- mixture of the ketone **28** was prepared from a mixture of isomeric bromides **20** via reaction of the derived Grignard reagent with propanal and oxidation of the alcohol **30** with pyridinium chlorochromate. The ^{1}Hmr spectrum of this mixture of ketones was used to determine the isomeric purity of subsequent batches of the ketone **28**, and to optimize conditions for further transformations. Optimum conditions for the conversion of pure **27** to pure *E*-γ,δ-unsaturated ketone **28** were attained using barium hydroxide in aqueous ethanol under reflux. Thus a 75% yield of **28**, of >98% isomeric purity, was obtained (1). Homologation of **28** was accomplished via the nitrile **31** for which two routes were investigated. Firstly reduction of **28** (>98% *E*) with sodium borohydride in methanol gave **30** which was readily converted to the mesylate **32**. Reaction of the latter with sodium cyanide in HMPA gave a 60%

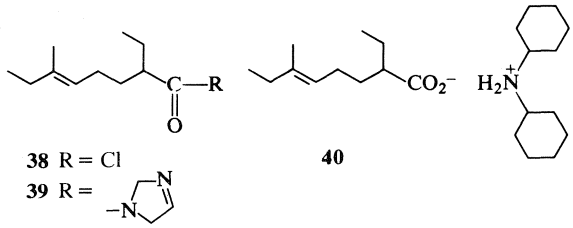
overall yield of **31** contaminated with ca. 9% *Z*-isomer as determined from the 270 MHz ^{1}Hmr spectrum. The obvious isomerization of *E* to *Z* in the sequence **28** → **30** → **32** → **31** dictated an alternative method of preparation of **31**. Success was achieved when **28** (>98% *E*) was reacted with potassium hydride and tosylmethylisocyanide (TOSMIC) (27–29) in DME. The nitrile **31** of ca 98% isomeric purity was isolated in 75% yield. Analogous reaction using potassium *tert*-butoxide in *tert*-butanol and DME gave nitrile of 95% isomeric purity. Hydrolysis of **31** (98% *E*) required heating to 180°C in a sealed tube with potassium hydroxide in aqueous methanol, and under these conditions acid **17** of ca. 87% isomeric purity (determined as above using ^{13}Cmr spectroscopy) was obtained in 74% yield. Treatment of **31** with powdered potassium hydroxide in refluxing dry *tert*-butanol (30) gave a 62% yield of the crystalline primary amide **33** (ca. 93% *E*, 7% *Z*). Although recrystallization of **33** may have improved the isomeric purity, attempts to convert **33** to the acid **17** under mild conditions (aqueous sodium peroxide (31)) were unsuccessful. Thus although this route (Scheme 5) provided the required acid **17**, the subsequent conversion of a substrate of ca. 93% isomeric purity to juvenile hormone analogues was considered unsatisfactory.

An alternative route to the *E*-acid **17** is outlined in Scheme 6. In this regard, pure *E*-allylic chloride (1) **26** was reacted with phenylthiomethylcopper (32–35) in THF to give a mixture of the thioether **34** (75% by glc) and thioanisole **35** (20% by glc). This mixture was generally used as such for subsequent conversions. An analytical sample of **34** (94% *E* by 270 MHz ^{1}Hmr) was obtained by preparative glc. Another sample obtained by fractional distillation of the mixture, however, was similarly shown to be 98% *E*-isomer. Reaction of the mixture of **34** and **35** with iodomethane and sodium iodide in dimethylformamide (DMF) in the presence of metallic mercury and calcium carbonate (35) at 70°C gave, after dilution with ether, the precipitated salts **36** and **37** together with an ethereal solution of the unstable iodide **25**, thioanisole **35**, and the thioether **34** in the ratio 38:50:12 (as determined by glc). Separation of the iodide from the above mixture either by distillation or by preparative glc was not possible. Therefore the mixture was treated, as such, with the dianion from *n*-butanoic acid in THF and HMPA to give the acid **17** and a mixture of **34** and **35**. The separated neutral fraction was combined with the salts from the previous reaction and the cycle repeated. The ^{13}Cmr spectrum of **17** obtained via this route indicated 95% *E*-, 5% *Z*-isomer (24).



SCHEME 6

Although this synthesis had allowed generation of the acid **17** with high stereoselectivity, it was decided that for the purposes of biological screening of subsequently derived JH analogues, a higher isomer integrity was desirable. Therefore various methods of purification of **17** were investigated. A derivative of the acid was sought such that purification would enable separation of pure *E*-isomer and such that efficient regeneration of acid could be accomplished without concomitant alkene isomerisation. The crystalline amide **33** was also available via the acid chloride **38** but, as mentioned above, regeneration of **17** under mild conditions was not possible. The methyl ester was a liquid, as expected, and separation of the *E*- and *Z*-isomers using glc or conventional chromatographic methods (including silver nitrate impregnated silica gel (36)) was not accomplished. Imidizolides were reported (37) to generally exhibit good crystalline properties; however, the derivative **39** derived from **17** was a liquid. Both the ammonium and dimethylammonium salts were crystalline but relatively unstable, each liberating the acid **17** and the respective amine on standing. The crystalline diisopropylammonium salt was stable but recrystallization even from *n*-hexane at −78°C was quite inefficient. The derivative of choice proved to be the dicyclohexylammonium salt **40**, which could be readily formed and which quantitatively liberated the acid **17** on treatment with cold, dilute hydrochloric acid in methanol solution without



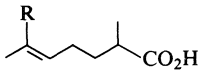
38 R = Cl
39 R =

40

observable *E*-/*Z*- isomerisation. This salt was obtained in stable crystalline form and could be recrystallised from ethyl acetate, 2-butanone, or, more efficiently, from acetone.

A sample of **17** (95% *E*, 5% *Z*) prepared via the route depicted in Scheme 6 was converted to the salt **40** and this derivative recrystallized four times from acetone to give a sample of mp 81.5–82°C. Regeneration of the acid **17** (48% recovery overall) gave a sample of 98% isomeric purity (as determined by ^{13}Cmr). A sample of acid **17** (80% *E*, 20% *Z*), derived as indicated in Scheme 4, was purified as described above, with seven recrystallizations of the intermediate salt, to give a sample of 95% *E* purity. Severe losses of material in this procedure precluded the use of this latter route to the *E*-acid **17**.

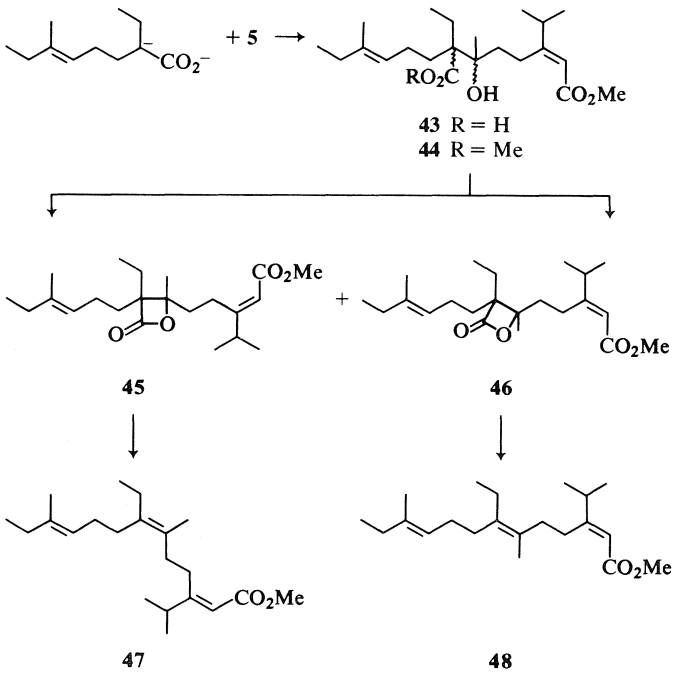
Of the methods examined, that involving the thioether **34** seemed to offer the best route to large quantities of **17** of suitable isomeric purity. Now with the chemistry to pure *E*-acid **17** in hand, its application to the corresponding *Z*-isomer **18** and to the acids **41** and **42**, related to the hormones **8**, **9** and **10**, is assured.



41 R = Et
42 R = Me

Prior to attempting the coupling reaction, several experiments were carried out to determine optimum conditions for formation of the acid dianion. Two bases were examined, lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) (38). The extent of α-anion formation was determined by quenching with D_2O and measuring the decrease in area related to the α-H resonance at δ 2.31 in the 270 MHz ^{1}Hmr spectrum of **17**. ^{13}Cmr spectroscopy was used to evaluate any concomitant *E*-/*Z*- isomerisation. In this manner optimum conditions were found (up to 79% dianion formation without detectable stereoisomerisation) using LDA in THF at 50°C for four hours, followed by quenching at 0°C. These conditions were subsequently used for the coupling reaction.

In the event, coupling of pure *E*-acid **17** with the more readily available (*E*)-β-thujaketonic acid methyl ester (**5**) gave a mixture of diastereomeric β-hydroxy-acids **43** which was characterized as the methyl esters



43 R = H
44 R = Me

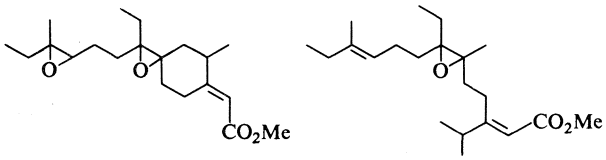
45 **46**

47 **48**

SCHEME 7

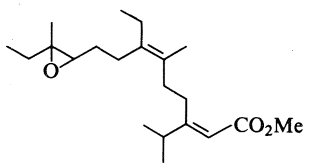
44 obtained by reaction with diazomethane in ether at 0°C. Alternatively reaction of the crude hydroxy-acids with benzenesulphonyl chloride at 0°C in pyridine gave a mixture of the two diastereomeric β-lactones **45** and **46** in the ratio 45:55 (i.e., ratio of the corresponding trienes **47** and **48** formed by pyrolytic cleavage during glc examination). Chromatographic separation on silica gel afforded the individual isomeric lactones. Subsequent pyrolysis of **45** in refluxing methylcellusolve gave the less polar triene-ester **47**. Similarly **46** was efficiently converted to **48**. The coupling reaction was then repeated on a mixture of *E*- and *Z*-acids **17** and **18** (ratio 80:20) and the product converted to a mixture of the isomeric β-lactones. Analysis of this four component mixture both by tlc and glc showed only two components (viz. **45** and **46**) thus confirming the necessity for pure *E*- (or *Z*-) acid as substrate.

Although a variety of methods have appeared for the selective epoxidation (39–47) of trisubstituted alkenes near the terminus of a polyene chain, here the extra activity of an internal tetrasubstituted double bond was expected to preclude any such selection. These suspicions were justified as shown by a trial epoxidation of the triene-ester **47**. Reaction of **47** with one equivalent of *meta*-chloroperbenzoic acid (*m*CPBA) at 0°C gave a mixture of **47**, the bis-epoxide **49**, and a mixture (70:30) of the mono-epoxides **50** and **51**.



49

50



51

The dividends from the choice of the acid dianion coupling mode were now apparent as similar epoxidation of the separated β-lactones **45** and **46** gave a high yield of epoxy-lactones **52** and **53** respectively. Pyrolysis of **52** in refluxing methylcellusolve gave **51**. Similarly **53** gave the juvenile hormone analogue **54** in high yield.

Experimental

Uncorrected melting points were determined on a Reichert micro hot stage. Boiling points are uncorrected. Infrared spectra were recorded on either a Perkin–Elmer 710 or 457 spectrophotometer. ^{1}Hmr spectra were recorded on a Varian T-60, HA-100, or XL-100, or a 270-MHz spectrometer in $CDCl_3$ solution, with tetramethylsilane as internal standard. Isomer ratios were determined by weighing respective peaks of an expanded spectrum run at 270 MHz. Mass spectra were recorded on an Atlas CH-4B or AEI MS-902 instrument. Microanalyses were carried out by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia. ^{13}Cmr spectra were measured on a Varian CFT-20 instrument. Analytical glc separations were carried out on a Hewlett Packard 5830A gas chromatograph. Preparative glc separations utilized a Varian model 90-P gas chromatograph. Column chromatography utilized Merck silica gel 60 (70–230 mesh) or Merck aluminum oxide 90 (neutral). Preparative and thin layer chromatography utilized Merck silica gel GF_{254}.

As a matter of routine, all reagents and solvents were recrystallized or distilled prior to use.

The Hydroxyacid ***14***

A solution of cyclohexane carboxylic acid (93 mg) in dry tetrahydrofuran (5 mL) was added at −78°C to a solution of lithium diisopropylamide (2 equiv.) in dry tetrahydrofuran (2 mL) and the mixture warmed to 50°C for 1.5 h under an atmosphere of dry nitrogen. The solution was cooled to ca. 20°C and then added slowly to a solution of (*E*)-β-thujaketonic acid methyl ester (**5**) (150 mg) in dry tetrahydrofuran at −78°C. The solution was stirred at this temperature for 30 min, warmed to ca. 20°C and neutralized with methanolic hydrochloric acid. The mixture was diluted with water and extracted with dichloromethane. The extract was washed with 5% sodium bicarbonate solution, the washings acidified and extracted with dichloromethane. This extract was dried ($MgSO_4$) and evaporated to give the hydroxy acid **14** (150 mg, 64%) as a colourless oil; ir ν_{max}: 3350, 3300–2400, 1700, 1640; ^{1}H nmr δ: 8.3 (2H, broad envelope, D_2O exchangeable, —CO_2H and —OH), 5.66 (1H, s, —C=C$H$$CO_2CH_3$), 3.70 (3H, s, —$CO_2CH_3$), 1.25 (3H, s, —C(OH)C$H_3$), 1.10 (6H, d, J = 7 Hz, —CH(CH_3)$_2$); ms *m/e*: 311 (M^+ − CH_3), 283, 199, 167, 139.

The β*-Lactone* ***15***

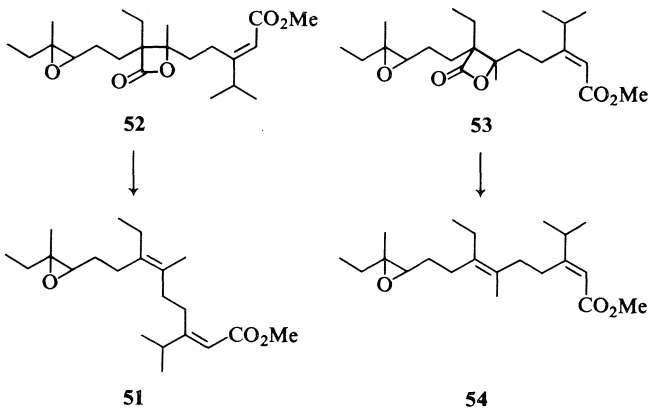
Benzenesulphonyl chloride (200 mg) was added to a solution of the hydroxyacid **14** (110 mg) in dry pyridine (5 mL) at −5°C. The mixture was allowed to stand at ca. 0°C overnight, poured into ice-water and extracted with ether. The extract was washed with 5% sodium bicarbonate solution, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel gave the β-lactone **15** (65 mg, 65%) as a colourless oil; ir ν_{max}: 1810, 1710, 1650; ^{1}H nmr δ: 5.70 (1H, s, —C=C$H$$CO_2CH_3$), 3.70 (3H, s, —$CO_2CH_3$), 1.78 (3H, s, —C(OR)C$H_3$), 1.10 (6H, d, J = 7 Hz, —CH(CH_3)$_2$); ms *m/e*: 264 (M^+ −CO_2), 233, 221, 142.

The Ester ***16***

The β-lactone **15** (60 mg) was heated to 140°C for 1.5 h in a nitrogen atmosphere. Chromatography on silica gel gave the olefin **16** (35 mg, 68%) as a colourless oil; ir ν_{max}: 1710, 1640; ^{1}H nmr δ: 5.70 (1H, s, —C=C$H$$CO_2CH_3$), 3.70 (3H, s, —O$CH_3$), 1.75 (3H, s, —$CH_3$), 1.10 (6H, d, J = 7 Hz, —CH-(CH_3)$_2$); ms *m/e*: 264 (M^+), 233, 221, 142, 123.

The Alcohol ***19***

Ethyl bromide (26 g) in dry ether (25 mL) was added to magnesium turnings (7.51 g) in dry ether (75 mL) under dry nitrogen, and the mixture refluxed for 1.5 h. The solution was cooled to ca. 0°C and cyclopropyl methyl ketone (17 g) added during 30 min. The mixture was stirred at ambient temperature for 16 h, diluted with cold, saturated ammonium chloride solution, and extracted with ether. The extract was washed with brine, dried (K_2CO_3), and concentrated at atmospheric pressure. The crude product was distilled between 43 and 67°C at 60 Torr to give pure (glc, 7% Carbowax 1500 on 90–100 mesh Anakrom ABS) carbinol **19** (18.34 g, 80%); ir (film) ν_{max}:



SCHEME 8

3400, 3080; ^{1}Hmr δ: 1.57 (2H, q, J = 7.4 Hz, —CH_2CH$_3$), 1.09 (3H, s, —CH$_3$), 0.98 (3H, t, J = 7.4 Hz, —CH$_2$CH_3), 0.35 (m, cyclopropyl —H); ms m/e: 99 (M − 15), 85.

(E)- *and* (Z)-*6-Bromo-3-methyl-3-hexene (20)*

A solution of 1,2-dibromoethane (18.2 mL) in dry ether was added slowly, at 0°C, to magnesium turnings (5.63 g) in ether (100 mL). After complete addition (1.5 h) the mixture was heated to reflux for 1 h, then stirred at ambient temperature for 16 h. A solution of the alcohol **19** (6.16 g) in dry ether (25 mL) was added and the mixture refluxed for 1.5 h, then stirred at ambient temperature for 6 h. The mixture was cooled and carefully washed with brine. The ethereal layer was dried (Na_2SO_4) and evaporated to give an oil (9.46, g, 98%) which appeared homogeneous by tlc and by glc. This product was distilled at 75°C, 10 Torr to give *E*- and *Z* homoallylic bromides **20**; ir ν_{max}: 2970, 2930, 2880, 1670, 1460, 1380, 1275; ^{1}Hmr ($CDCl_3$) δ: 5.16 (1H, complex multiplet, C4-H), 3.36 (2H, t, J = 7 Hz, —CH_2Br), 2.58 (2H, q, J = 7 Hz, C5-H2), 2.04 (2H, q, J = 7 Hz, C2-H2), 1.64 (3H, bs, C3-CH$_3$), 1.00 (3H, t, J = 7 Hz, —CH$_2$CH_3). An *E*/*Z* ratio of 3:1 was determined from the areas under the vinylic methyl signals for the *E*- (δ 1.64) and *Z*- (δ 1.72) isomers.

The Esters 21

n-Butyllithium (0.6 mL of a 2.83 M solution in pentane) was added to a solution of diisopropylamine (0.17 g, 0.24 mL) in dry THF (1.7 mL) at 4°C. The solution was stirred at this temperature for 15 min and then cooled to −78°C. Methyl butanoate (0.173 g) was added and the mixture stirred for 40 min at −78°C. A solution of the bromides **20** (0.36 g) in HMPA (0.15 mL) was added and the mixture stirred at −78°C for 30 min, then at ambient temperature for 1.5 h, poured onto ice cold 1 M HCl and extracted with ether. The ethereal extract was dried (Na_2SO_4) and evaporated. Chromatography on alumina gave the esters **21** (0.08 g, 20%); ir ν_{max}: 1720; ^{1}Hmr ($CDCl_3$) δ: 5.10 (1H, bm, C5-H), 3.72 (3H, s, —OCH$_3$).

The Oxazolines 23

n-Butyllithium (0.48 mL of 2.7 M solution in *n*-pentane) was added slowly to a solution of the propyloxazoline **22** (172 mg) in dry THF at −78°C. The yellow solution was stirred at this temperature under a nitrogen atmosphere for 30 min and then treated with the bromides **20** (255 mg). The mixture was kept at −78°C for 30 min and then allowed to attain ambient temperature. The mixture was partitioned between brine and ether, the ethereal layer dried (Na_2SO_4), and evaporated. The residue was distilled at 70°C, 0.1 Torr to give the oxazolines **23** (322 mg, 94%); ^{1}Hmr ($CDCl_3$) δ: 5.17 (1H, bm, vinylic —H), 3.94 (2H, bs, —O—CH$_2$—), 1.64 (3H, bs, vinylic —CH$_3$), 1.33 (6H, bs, >C(CH$_3$)$_2$), 1.03 (3H, t, J = 7 Hz, —CH$_2$CH_3), 0.97 (3H, t, J = 7 Hz, —CH$_2$CH_3), plus small signals attributable to the *Z*-isomer; ms m/e: 237 (M$^+$), 222, 181, 154, 142, 126.

The Aminoester 24

A mixture of the oxazolines **23** (70 mg) and iodomethane (1 mL) was allowed to stand at ambient temperature for 20 h, the solvent was removed *in vacuo*, and the residue triturated with ether to afford the methiodide salt. This solid was dissolved in 1 M NaOH (5 mL) and the solution stirred at ambient temperature for 20 h. The mixture was diluted with water and extracted with petroleum ether. The organic layer was dried and concentrated to give **24** (60 mg); ir ν_{max}: 3300, 1725; ^{1}Hmr ($CDCl_3$) δ: 5.00 (1H, bm, vinylic —H), 3.82 (2H, s, —OCH$_2$—), 2.31 (3H, s, —NCH$_3$), 1.51 (3H, bs, vinylic —CH$_3$), 1.08 (6H, s, —C(CH$_3$)$_2$).

The Acids 17 and 18

From 24

The ester **24** was heated to 50°C for 17 h in a mixture of 6 M NaOH and ethanol. The mixture was acidified with 1 M HCl and extracted with ether to give (48%) the acids **17** and **18** (see below).

From 20

n-Butyllithium (2.0 mL of 2.82 M solution in pentane) was added to a cold (−15°C) solution of diisopropylamine (0.8 mL, 0.58 g) in dry THF (4.5 mL) and the mixture stirred for 15 min. Dry *n*-butyric acid (0.25 mL, 0.24 g) was added and the mixture stirred at ca. 0°C for 20 min. The *E*/*Z*-bromides **20** (0.5 g) in dry HMPA (1 mL) were added and the solution stirred at 0°C for 10 min, then at ambient temperature for 30 min. The mixture was carefully acidified and partitioned between ether and brine. The ether extracts were washed with brine (×2), dried and concentrated. Distillation of the residue (115°C, 0.3 Torr) gave the acids **17** and **18** (0.25 g, 48%), (see below).

The Iodides 25

From 20

The bromides **20** (0.366 g) and dry sodium iodide (0.150 g) in dry acetone (1 mL) were heated to reflux in the presence of $CaCO_3$ and mercury (35). After 30 min the mixture was cooled, filtered, and concentrated *in vacuo*. Distillation of the residue at 30°C/0.1 Torr gave the iodides **25** (0.254 g, 55%).

From 19 (17, 18)

The carbinol **19** (11.8 g) in dry ether (200 mL) was added slowly to a solution of magnesium iodide (4 equiv.) in dry ether and the mixture refluxed for 5 h under a nitrogen atmosphere. After a further 16 h at ambient temperature, the reaction was carefully quenched with cold water and then extracted

with petroleum ether (30–60°C). The organic extract was washed with brine. dried (Na_2SO_4), and concentrated *in vacuo* to give the *E*-/*Z*-iodides **25** (23 g, 100%) homogeneous by glc (5% OV 17), bp 40°C/0.1 Torr; ^{1}Hmr ($CDCl_3$) δ: 0.97 (3H, t, J = 7.5 Hz, —CH_2CH_3 *Z*-isomer), 0.99 (3H, t, J = 7.5 Hz, —CH_2CH_3 *E*-isomer), 1.60 (3H, s, —CH_3 *E*-isomer), 1.68 (3H, d, J = 1.1 Hz, —CH_3 *Z*-isomer), 2.0 (2H, m, —CH_2CH_3), 2.57 (2H, m, —CH_2CH_2I), 3.09 (2H, m, —CH_2I), 5.08 (1H, m, vinylic —H). Ratio by ^{1}Hmr (methyl group resonances) *E*/*Z* ca. 3:1.

*The Acids **17** and **18** from **25***

A solution of *n*-butyllithium in hexane (75.2 mL of 1.72 *M*) was added to a mixture of anhydrous diisopropylamine (11.9 g) and dry THF (96 mL) at −78°C under a nitrogen atmosphere. The mixture was stirred at −78°C for 30 min and then warmed to −23°C. At this temperature, *n*-butyric acid (4.71 g) was added and the mixture stirred for 30 min. The temperature was raised to 0°C and dry HMPA (10.5 g) added. After 40 min, the iodides **25** (6.1 g) were added and the solution stirred for 20 h at ambient temperature. The mixture was acidified with cold 1 *N* HCl and extracted with petroleum ether (30–60°C). The organic layer was then extracted with ice cold 1 *N* NaOH, the alkaline layer neutralised with 1 *N* HCl, and extracted with petroleum ether. This organic extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Distillation of the residue at 90°C/0.1 Torr gave the isomeric acids **17** and **18** (3.88 g, 79%), homogeneous by glc (5% OV 17); ir ν_{max}: 3400–2400, 1705; ^{1}Hmr ($CDCl_3$) δ: 5.09 (1H, m, C5-H), 2.31 (1H, m, C2-H), 2.00 (4H, m, C7-H2 and C4-H2), 1.60 (4H, m, C3-H2 and C2-CH_2CH_3), 1.66 (3H, s, vinylic —CH_3, *Z*-isomer), 1.58 (3H, s, vinylic —CH_3, *E*-isomer), *E*/*Z* ratio by vinylic —CH_3 signals ca. 3:1; ^{13}Cmr (^{1}H, noise decoupled) ($CDCl_3$) δ: 182.9 (C1), 138.1 (C6, *Z*-isomer), 137.9 (C6, *E*-isomer), 123.3 (C5, *Z*-isomer), 122.0 (C5, *E*-isomer), *E*/*Z* ratio by C5 signal = 4:1; ms *m*/*e*: 184.1454 (M^+, $C_{11}H_{20}O_2$ requires 184.1463), 183, 166, 155, 138, 109. *Anal.* calcd. for $C_{11}H_{20}O_2$: C 71.70, H 10.94; found: C 71.92, H 10.86. NB the discrepancy in the ratios derived by ^{13}C and ^{1}Hmr was apparently due to overlap of the vinylic —CH_3 signals with a broad multiplet. The ratio derived from the ^{13}Cmr spectrum utilised signals with clean, baseline separation.

*The Alcohol **30***

The bromides **20** (3.19 g) and magnesium turnings (0.46 g) were allowed to stir in dry ether (2 mL) for 5 h. Propanal (0.966 g) was added and the stirring continued for 12 h at ambient temperature. The mixture was carefully quenched with water, dried (Na_2SO_4), and concentrated *in vacuo* to give **30** (2.16 g, 83%), identical (by glc) with an authentic sample (1).

*The Ketone **28** from **30***

Oxidation of **30** according to the literature (48) procedure gave the ketone **28** (71%) identical with an authentic sample (1).

*The Mesylate **32***

The alcohol **30** (200 mg) and methanesulphonyl chloride (900 mg) were stirred in dry pyridine (2 mL) at 0°C for 18 h. The mixture was poured into ice-water and extracted with dichloromethane. The extract was washed with brine, dried ($MgSO_4$), and evaporated to give the crude mesylate **32** (450 mg); ir ν_{max}: 1350, 1170; which was used without further purification.

*The Nitrile **31***

*From **32***

The crude mesylate **32** (450 mg) and sodium cyanide (300 mg) were stirred in dry hexamethylphosphortriamide (1 mL) under a nitrogen atmosphere for 15 h. The mixture was diluted with water and extracted with ether. The extract was washed with 1 *N* hydrochloric acid, water and brine, dried ($MgSO_4$), and evaporated. Chromatography on silica gel afforded the nitrile **31** (210 mg, 60% from **30**); ir (film) ν_{max}: 2230, 1668; ms *m*/*e*: 165 (M^+), 150, 137, 122. High resolution molecular weight determination calcd. for $C_{11}H_{19}N$: 165.1517; found: 165.1525. *Anal.* calcd. for $C_{11}H_{19}N$: C 79.94, H 11.59; found: C 80.20, H 11.52.

*From **28***

TOSMIC (29) (0.377 g) in dry DME (4 mL) was added to potassium hydride/mineral oil suspension (0.39 g, 4.99 mmol KH/g of suspension) in dry DME (4 mL) at −46°C under a nitrogen atmosphere. The mixture was stirred at this temperature for 10 min, then at 0°C for 10 min to give a bright yellow solution. Pure *E*-enone **28** (1) (0.175 g) in DME (4 mL) was added at 0°C and the solution stirred for 45 min. Anhydrous methanol (0.079 mL) was added and stirring continued for 1 h (0–5°C). The solution was then allowed to attain ambient temperature and methanol (0.21 mL) added. Stirring was continued for a further 88 h. The mixture was then diluted with water and extracted with *n*-pentane. The extract was washed with brine, dried (Na_2SO_4), and the solvents removed *in vacuo*. Chromatography of the residue on silica gel gave the *E*-cyanide **31** (0.14 g, 75%); bp 67–73°C/0.1 Torr; ^{1}Hmr ($CDCl_3$) δ: 5.08 (1H, t, J = 7.6 Hz, vinylic —H) 2.48 (1H, m, —CHCN i.e., C2-H), 1.63 (3H, s, vinylic —CH_3): ^{13}Cmr ($CDCl_3$) δ: 139.2 (C6), 122.25 (C1), 120.8 (C5). The *E*/*Z* ratio was 98:2 from signals due to the vinylic methyl groups in the 270 MHz ^{1}Hmr spectrum and by signals due to C5 in the ^{13}Cmr spectrum as before. A sample of **31** prepared similarly from the ketones (*E*/*Z* ratio 19:6) was likewise shown to contain the *E*- and *Z*-isomers in the ratio ca. 19:6 indicating no observable double bond isomerisation during this step.

*The Acids **17** and **18** from **31***

A sample of the nitrile **31** (0.054 g, 98% *E*-) and potassium hydroxide (0.09 g) in methanol (1 mL) and water (0.3 mL) were heated at 180°C (sealed tube) for 48 h. Usual work-up gave the acids **17** and **18** (0.042 g, 74%) in the ratio 87:13 determined as above by ^{13}Cmr spectroscopy.

*The Amide **33***

The nitrile **31** (98% *E*-, 0.05 g) and powdered, dry potassium hydroxide (0.06 g) were heated in refluxing, dry *tert*-butanol (0.5 mL) for 10 h. The usual work-up procedure gave the amide **33** (0.034 g, 62%); ^{1}Hmr ($CDCl_3$) δ: 6.22 (1H, s, —NH), 5.60 (1H, s, —NH), 1.66 (3H, s, vinylic —CH_3, *Z*-isomer), 1.58 (3H, s, vinylic —CH_3, *E*-isomer). *E*/*Z* ratio from vinylic methyl signals was 93:7.

*The Sulphide **34***

Pure *E*-chloride **26** (1) (3.6 g) was added to a solution of phenylthiomethylcopper (from 3.7 g of thioanisole) (32–34) in dry THF (28 mL) at −50°C under an atmosphere of nitrogen. The mixture was stirred at −50°C for 30 min, at −23°C for 3 h, then at ambient temperature for 60 h. The solution was diluted with water and extracted with petroleum ether (30–60°C). The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product (4.62 g) was shown (glc, 5% OV17) to comprise thioanisole (20%) and product (75%). An analytical sample of **34** was obtained by preparative glc; ir ν_{max}: 3060, 3045, 1660, 1580, 735, 688; ^{1}Hmr ($CDCl_3$) δ: 7.22 (5H, m, Ar —H), 5.16 (1H, m, vinylic —H), 2.90 (2H, t, J = 6.5 Hz, —$CH_2SC_6H_5$), 1.68 (3H, s, vinylic —CH_3, *Z*-isomer), 1.57 (3H, s, vinylic —CH_3, *E*-isomer), *E*/*Z* ratio: 47:3; ms *m*/*e*: 206.1124 (M^+, $C_{13}H_{18}S$ requires 206.1129), 136, 123. *Anal.* calcd. for $C_{13}H_{18}S$: C 75.69, H 8.80; found: C 75.86, H 8.70.

A small sample obtained by distillation (85°C/0.1 Torr) was similarly shown to have an *E*/*Z* ratio of 49:1.

*The Iodide **25** from **34***

The crude thioether **34** (containing thioanisole, 4.1 g), dry

sodium iodide (10.7 g), calcium carbonate (0.156 g), and mercury (1 drop) were mixed in dry DMF (42 mL). Iodomethane (32.3 mL) was added and the mixture heated at 60–75°C for 28 h under an atmosphere of dry argon. The mixture was then cooled to ca. 20°C, diluted with ether, and cooled to ca. 0°C. The crystalline material was removed by filtration, dried, and reserved for recycling. The filtrate was washed with brine, dried (Na_2SO_4), and the solvents removed by distillation at atmospheric pressure (60–70°C). Gas–liquid chromatographic analysis (5% OV17) of the residue (0.68 g) indicated iodide **25** (38%), thioanisole (49%), and thioether **34** (12%). The iodide thus obtained was not purified but used as such for the next step.

*The Acid **17** from **25***

The dianion of *n*-butyric acid (1.4 g) was alkylated, as described earlier, with the crude **25** (1.8 g) to give (**17**) (0.924 g). The *E*/*Z* ratio in this product was found to be 95:5 by ^{13}Cmr as before. The neutral fraction (2.7 g) from the work-up of this reaction, shown by glc to contain thioanisole (56%) and the thioether (42%), was reserved for recycling.

*Purification of **17** via **40***

Dicyclohexylamine (2.98 g, 3.28 mL) was added to a solution of the acid **17** (95% *E*-, 2.88 g) in *n*-hexane. The mixture was cooled to −78°C and the crystalline product **40** collected by filtration. The salt was recrystallized (× 5) from acetone to give material with mp 81.5–82°C.

The salt **40** was then dissolved in methanol containing ca. 10% HCl at 0°C. The mixture was stirred for 5 min, diluted with ice cold water, and extracted with petroleum ether (30–60°C). The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Distillation of the residue gave **17** (1.38 g). The *E*/*Z* ratio was determined as 49:1 by ^{13}Cmr spectroscopy.

*The Hydroxyacid **43***

n-Butyllithium (5.9 mL, 1.70 *M*) was added to a solution of diisopropylamine (0.922 g, 1.28 mL) in dry THF (6.3 mL) at −78°C under a nitrogen atmosphere, and the mixture stirred for 1 h at this temperature, then at −23°C for 20 min. A solution of the *E*-acid **17** (0.763 g) in dry THF (1 mL) was added and the solution stirred at −23°C for 30 min, then at 0°C for 10 min. The mixture was heated to 50°C for 4 h, and then cooled to −78°C. A solution of the ketoester **5** (0.827 g) in dry THF (1 mL) was added slowly, and the mixture warmed (over 2 h) to 0°C, poured into ice-water, and extracted with petroleum ether (30–60°C). The extract was dried and concentrated to give **5** (0.293 g). The aqueous layer was adjusted to pH 1 with ice cold 1 *N* HCl and then extracted with petroleum ether (30–60°C). This extract was washed with brine, dried, and concentrated to give the hydroxyacid **43** (1.37 g); ir ν_{max}: 3450–2600, 1710, 1700, 1640; ^{1}Hmr ($CDCl_3$) δ: 8.0 (2H, bs, —OH and —CO_2H), 5.60 (1H, s, C=C*H*CO_2Me), 5.05 (1H, bt, vinylic —H), 3.65 (3H, s, —OCH_3), 1.6 (3H, s, vinylic —CH_3), 1.3 (3H, s, —CH_3); ms *m*/*e*: 382.2717 (M^+, $C_{22}H_{38}O_5$ requires 382.2719), 381, 269, 251, 219, 199, 184, 167, 96.

*The Ester **44***

A sample of the crude **43** (60 mg) was esterified with diazomethane in ether to give, after chromatography on silica gel, the ester **44** (27 mg, 44%); ir ν_{max}: 3470, 1715, 1640, 1170; ^{1}Hmr ($CDCl_3$) δ: 5.60 (1H, s, C=C*H*CO_2Me), 5.06 (1H, bt, vinylic —H), 3.63 (3H, s, —OCH_3), 3.60 (3H, s, —OCH_3), 3.50 (1H, bs, —OH), 1.60 (3H, s, vinylic —CH_3), 1.23 (3H, s, —CH_3), 1.08 (6H, d, J = 7 Hz, —CH(CH_3)$_2$); ms *m*/*e*: 396 (M^+), 381, 315, 283, 251, 218, 167, 166. *Anal.* calcd. for $C_{23}H_{40}O_5$: C 69.66, H 10.17; found: C 69.93, H 10.33.

*The β-Lactones **45** and **46***

The crude hydroxyacid **43** (1.37 g) and benzenesulphonyl chloride (0.27 g) were stirred in dry pyridine (3 mL) at 0–5°C for 18 h. The mixture was poured into ice-water and extracted with dichloromethane. The extract was washed with sodium bicarbonate solution, brine, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography on silica gel at ca. 5°C gave the lactone **46** (0.51 g, 39%); ir ν_{max}: 1810, 1715, 1640, 1170; ^{1}Hmr ($CDCl_3$) δ: 5.68 (1H, s, —C=C*H*CO_2CH_3), 5.09 (1H, bt, vinylic —H), 3.64 (3H, s, —OCH_3), 1.59 (6H, s, 2 × —CH_3), 1.07 (6H, d, J = 7 Hz, —CH(CH_3)$_2$); and the lactone **45** (0.49 g, 38%); ir ν_{max}: 1810, 1715, 1640, 1170; ^{1}Hmr ($CDCl_3$) δ: 5.67 (1H, s), 5.07 (1H, bt), 3.63 (3H, s), 1.57 (6H, s), 1.07 (6H, d, J = 7 Hz). Each isomer was homogeneous by glc (OV17).

*The Triene **47***

The lactone **45** (0.49 g) was heated in refluxing 2-methoxyethanol (20 mL) for 1 h under a nitrogen atmosphere. The solvent was removed *in vacuo* to give, after distillation at 120°C/0.1 Torr, the triene ester **47** (0.39 g, 91%); ir ν_{max}: 1720, 1640, 1175; ^{1}Hmr ($CDCl_3$) δ: 5.66 (1H, s, —C=C*H*CO_2CH), 5.16 (1H, bs, vinylic —H), 3.70 (3H, s, —OCH_3), 1.73 (3H, s, —CH_3), 1.57 (3H, s, —CH_3), 1.10 (6H, d, J = 7 Hz, —CH(CH_3)$_2$); ^{13}Cmr ($CDCl_3$) δ: 170.3 (C1), 167.2 (C3), 136.7 (C11), 135.3 (C7), 127.9 (C6), 123.2 (C10), 112.8 (C2), 50.8 (—O*C*H_3); ms *m*/*e*: 320.2708 (M^+, $C_{21}H_{36}O_2$ requires: 320.2715); *Anal.* calcd. for $C_{21}H_{36}O_2$: C 78.69, H 11.32; found: C 78.97, H 11.06.

*The Triene **48***

Similarly, the lactone **46** gave **48** (90%); ir ν_{max}: 1720, 1640, 1175; ^{1}Hmr ($CDCl_3$) δ: 5.62 (1H, s, —C=C*H*CO_2CH_3), 5.11 (1H, bs, vinylic —H), 3.65 (3H, s, —OCH_3), 1.71 (3H, s, —CH_3), 1.59 (3H, s, —CH_3), 1.07 (6H, d, J = 7 Hz, —CH(CH_3)$_2$); ^{13}Cmr ($CDCl_3$) δ: 170.2 (C1), 167.3 (C3), 136.8 (C11), 135.3 (C7), 127.9 (C6), 123.1 (C10), 112.8 (C2), 50.8 (—O*C*H_3); *Anal.* calcd. for $C_{21}H_{36}O_2$: C 78.69, H 11.32; found: C 78.79, H 11.40.

In the ^{13}Cmr spectra of the trienes **47** and **48** signals for C10 of the 10(11) *Z*-isomers (δ 124.3) were not observable. Furthermore each was homogeneous by glc (5% OV17, 180°C) analysis.

*The Epoxides **49**, **50**, and **51** from **47***

The triene ester **47** (0.05 g) and *m*CPBA (0.027 g) were stirred in chloroform (3 mL) at 0°C for 5 h. Chromatography on silica gel gave triene ester **47** (0.019 g) and a mixture (0.014 g) of **50** and **51**; ir ν_{max}: 1710, 1640; ^{1}Hmr ($CDCl_3$) δ: 5.65 (1H, s, —C=C*H*CO_2CH_3), 5.12 (1H, bt, vinylic —H for **50**), 3.68 (3H, s, —OCH_3), 1.60 (3H, s, vinylic —CH_3 for **50**), 1.41 (3H, s, —CH_3 for **50**), 1.09 (6H, d, J = 7.5 Hz, —CH(CH_3)$_2$ for **51**), 1.12 (6H, d, J = 7.5 Hz, —CH(CH_3)$_2$ for **50**); ratio of **50**/**51** ca. 7:3 from signals at δ 1.12 and 1.09 ppm; ms *m*/*e* 336.2641 (M^+, $C_{21}H_{36}O_3$ requires: 336.2664); and the bisepoxide **49** (0.016 g); ir ν_{max}: 1720, 1640; ^{1}Hmr ($CDCl_3$) δ: 5.65 (1H, s, —C=C*H*CO_2CH_3), 3.67 (3H, s, —OCH_3), 1.41 (3H, s, C6-CH_3), 1.24 (3H, s, C11-CH_3), 1.07 (6H, d, J = 7 Hz, —CH(CH_3)$_2$); ms *m*/*e* 352.2615 (M^+, $C_{21}H_{36}O_4$ requires: 352.2614).

*The Lactone **52***

Reaction of **45** with *m*CPBA (1.5 equiv.) in dichloromethane below 0°C gave, after chromatography on silica gel, the epoxide **52** in 92% yield; ir ν_{max}: 1810, 1710, 1640; ^{1}Hmr ($CDCl_3$) δ: 5.72 (1H, s, C2-H), 3.69 (3H, s, —OCH_3), 1.62 (3H, bs, C6-CH_3), 1.24 (3H, bs, C11-CH_3), 1.09 (6H, d, J = 7.5 Hz, C3-CH(CH_3)$_2$), 0.95 (6H, two overlapping triplets, —CH_2CH_3); homogeneous by glc (5% OV17, 180°C).

*The Lactone **53***

Similarly, **46** gave (91%) the lactone **53**; ir ν_{max}: 1810, 1710, 1640; ^{1}Hmr ($CDCl_3$) δ: 5.73 (1H, s, C2-H), 3.71 (3H, s,

—OCH_3), 1.64 (3H, s, C6-CH_3), 1.27 (3H, s, C11-CH_3), 1.10 (6H, d, J = 7.5 Hz, C3-CH(CH_3)$_2$), 0.97 (6H, two overlapping triplets, —CH_2CH_3); homogeneous by glc (5% OV17, 180°C).

The Epoxide 51

The lactone **52** was heated in refluxing 2-methoxyethanol under a nitrogen atmosphere for 2 h. The solvent was evaporated *in vacuo* and the residue purified by molecular distillation at 130°C, 0.5 Torr to give a quantitative yield of the epoxide **51**; ir ν_{max}: 1710, 1640; ^{1}Hmr ($CDCl_3$) δ: 5.64 (1H, s, C2-H), 3.68 (3H, s, —OCH_3), 2.74 (1H, t, J = 6 Hz, C10-H), 2.40 (1H, quintet, J = 7.5 Hz, —$CH(CH_3)_2$), 1.73 (3H, s, C6-CH_3), 1.22 (3H, s, C11-CH_3), 1.09 (6H, d, J = 7.5 Hz, —CH(CH_3)$_2$), 0.95 (3H, t, J = 7.5 Hz, —CH_2CH_3), 0.94 (3H, t, J = 7.5 Hz, —CH_2CH_3); ms *m/e* 336 (M^+), 318, 304, 289, 218, 202, 177, 121, 109. High resolution molecular weight determination, calcd. for $C_{12}H_{36}O_3$: 336.2664; found: 336.2660. *Anal.* calcd. for $C_{21}H_{36}O_3$: C 74.95, H 10.78; found: C 75.10, H 10.81.

The Epoxide 54

Similarly, **53** gave the epoxide **54**; ir ν_{max}: 1710, 1640; ^{1}Hmr ($CDCl_3$) δ: 5.64 (1H, s, C2-H), 3.68 (3H, s, —OCH_3), 2.72 (1H, t, J = 6 Hz, C10-H), 2.39 (1H, quintet, J = 7.5 Hz, —$CH(CH_3)_2$), 1.74 (3H, s, C6-CH_3), 1.24 (3H, s, C11-CH_3), 1.08 (6H, d, J = 7.5 Hz, —CH(CH_3)$_2$), 0.98 (3H, t, J = 7.5 Hz, —CH_2CH_3), 0.94 (3H, t, J = 7.5 Hz, —CH_2CH_3); ms *m/e* 336 (M^+), 318, 304, 289, 275, 218, 203, 177, 121, 109, 57. High resolution molecular weight determination, calcd. for $C_{21}H_{36}O_3$: 336.2664; found: 336.2676. *Anal.* calcd. for $C_{21}H_{36}O_3$: C 74.95, H 10.78; found: C 74.74, H 10.64.

Acknowledgements

Financial aid from the National Research Council of Canada is gratefully acknowledged. The authors would also like to thank MacMillan Bloedel Limited for generous supplies of thujone.

1. J. P. Kutney, J. Balsevich, R. Carruthers, Arie Markus, M. J. McGrath, R. N. Young, and B. R. Worth. Bioorg. Chem. **7**, 289 (1978).
2. J. Werner and M. T. Bogert. J. Org. Chem. **3**, 578 (1939).
3. N. Kornblum, S. D. Boyd, H. W. Pinnick, and R. G. Smith. J. Am. Chem. Soc. **93**, 4316 (1971).
4. A. P. Krapcho and E. G. E. Jahngen. J. Org. Chem. **39**, 1322 (1974); **39**, 1650 (1974).
5. M. Julia and J. M. Paris. Tetrahedron Lett. 4833 (1973).
6. G. H. Posner, G. L. Loomis, and H. S. Sawaya. Tetrahedron Lett. 1373 (1975).
7. S. Hara, H. Taguchi, H. Yamamoto, and H. Nozaki. Tetrahedron Lett. 1545 (1975).
8. J. E. McMurray and L. R. Krepski. J. Org. Chem. **41**, 3929 (1976).
9. W. Dumont and A. Krief. Angew. Chem. Int. Ed. Engl. **15**, 161 (1976).
10. N. Kornblum and L. Cheng. J. Org. Chem. **42**, 2944 (1977).
11. G. W. Moersch and A. R. Burkett. J. Org. Chem. **36**, 1149 (1971).
12. D. J. Humphreys and C. E. Newall. J. Chem. Soc. Perkin Trans. I, 33 (1978).
13. J. P. McCormick and D. L. Barton. J. Chem. Soc. Chem. Commun. 303 (1975).
14. M. Julia and J. M. Paris. Tetrahedron Lett. 3445 (1974).
15. M. Julia, S. Julia, and R. Guégan. Bull. Soc. Chim. Fr. 1072 (1960).
16. M. Julia, S. Julia, and S. Y. Tchen. Bull. Soc. Chim. Fr. 1849 (1961).
17. E. C. Ashby and R. C. Arnott. J. Organomet. Chem. **14**, 1 (1968).
18. L. F. Fieser and M. Fieser. Reagents for organic synthesis. Vol. 1. J. Wiley & Sons. 1967.
19. J. A. MacPhee and J. E. Dubois. J. Chem. Soc. Perkin Trans. I, 694 (1977).
20. D. F. Sullivan, R. P. Woodbury, and M. W. Rathke. J. Org. Chem. **42**, 2038 (1977).
21. A. I. Meyers and E. D. Mihelich. Angew. Chem. Int. Ed. Engl. **15**, 270 (1976).
22. A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich. J. Org. Chem. **39**, 2778 (1974).
23. P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr. J. Org. Chem. **37**, 451 (1972).
24. J. W. Blunt and M. H. G. Munro. Aust. J. Chem. **29**, 975 (1976).
25. H. Roller, K. H. Dahm, C. C. Sweeley, and B. M. Trost. Angew. Chem. **79**, 190 (1967); Angew. Chem. Int. Ed. Engl. **6**, 179 (1967).
26. G. W. Anderson, I. F. Halverstadt, W. H. Miller, and R. O. Roblin, Jr. J. Am. Chem. Soc. **67**, 2197 (1945).
27. O. H. Oldenziel and A. M. van Leusen. Tetrahedron Lett. 1357 (1973).
28. U. Schöllkopf and R. Schröder. Angew. Chem. Int. Ed. Engl. **12**, 407 (1973).
29. O. H. Oldenziel, D. van Leusen, and A. M. van Leusen. J. Org. Chem. **42**, 3114 (1977).
30. J. H. Hall and M. Gisler. J. Org. Chem. **41**, 3769 (1976).
31. H. L. Vaughn and M. D. Robbins. J. Org. Chem. **40**, 1187 (1975).
32. E. J. Corey and D. Seebach. J. Org. Chem. **31**, 4097 (1966).
33. R. L. Sowerby and R. M. Coates. J. Am. Chem. Soc. **94**, 4758 (1972).
34. E. J. Corey and G. H. Posner. J. Am. Chem. Soc. **89**, 3911 (1967).
35. E. J. Corey and M. Jautelat. Tetrahedron Lett. 5787 (1968).
36. A. S. Gupta and S. Dev. J. Chromatogr. **12**, 189 (1963).
37. H. A. Staab and W. Rohr. *In* Newer methods of preparative organic chemistry. Vol. 5. *Edited by* W. Foerst. Academic Press. 1968. p. 61.
38. R. A. Olofson and C. M. Dougherty. J. Am. Chem. Soc. **95**, 582 (1973).
39. P. A. Grieco, Y. Yo, S. Gilman, and M. Ni. J. Org. Chem. **42**, 2034 (1977).
40. E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson. J. Am. Chem. Soc. **90**, 5618 (1968).
41. E. E. Van Tamelin, M. A. Schwartz, E. Hessler, and A. Stone. J. Chem. Soc. Chem. Commun. 409 (1966).
42. E. E. Van Tamelin and T. J. Curphey. Tetrahedron Lett. 121 (1962).
43. K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui, and W. S. Bowers. Tetrahedron, **25**, 1667 (1969).
44. J. A. Findlay and W. D. MacKay. J. Chem. Soc. Chem. Commun. 733 (1969).
45. R. Breslow and L. M. Maresca. Tetrahedron Lett. 887 (1978).
46. K. H. Dahm, B. M. Trost, and H. Roller. J. Am. Chem. Soc. **89**, 5292 (1967).
47. W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell. J. Am. Chem. Soc. **90**, 6225 (1968).
48. E. J. Corey and J. W. Suggs. Tetrahedron Lett. 2647 (1975).