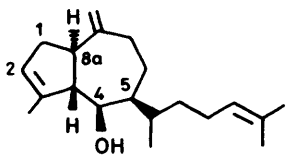
A Stereospecific Synthesis of Advanced Precursors of the Dictyol Diterpenes using the Alicyclic Claisen Rearrangement

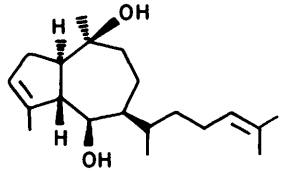
Michael J. Begley, Andrew G. Cameron, and David W. Knight*
Department of Chemistry, University of Nottingham, Nottingham NG7 2RD

Claisen rearrangements of the *O*-silyl enolates derived from macrolides (**15a**) and (**15b**) proceed stereospecifically to give the perhydroazulenes (**23a**) and (**24**), which contain appropriate functionality for further elaboration to members of the dictyol group of diterpenes [*e.g.*, dictyol C (**1**)]. The rearrangements proceed *via* a boat conformation (Scheme 1), as expected from previous model studies, in which the cyclopentyl residue is readily accommodated in a favourable *trans*-diequatorial position. The key *trans*-2,3-disubstituted cyclopentanone (**11a**) was prepared by a conjugate addition–trapping sequence from the dithiane (**10**), cyclopent-2-enone, and ethyl iodoacetate. Subsequent manipulation of the protecting groups then gave the hydroxy esters (**12a**) and (**14a**), which were directly lactonised to give the macrolides (**15a**) and (**15b**) *via* the corresponding lithium alkoxides.

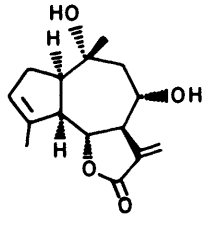
The dictyol diterpenes are a group of metabolites occurring in brown algae belonging to the Dictyotaceae family,[1] additional examples of which continue to be discovered.[2] The compounds of relevance to the work reported herein possess a perhydroazulene skeleton, and are exemplified by pachydictyol A (**1**) and dictyol C (**2**). Various other types of diterpenes isolated from these rich sources include examples based on the cyclononadiene, bicyclo[4.3.1]decane, and bicyclo-[7.2.0]undecane carbon frameworks.[2] Variations amongst the perhydroazulene-based dictyols arise from further oxygenation, typically at positions 1 or 7, or in the isoprenyl side-chain, together with structural modifications such as the formation of an ether bridge between C-4 and C-8. The central perhydroazulene feature of these diterpenes closely resembles that found in the more numerous sesquiterpene lactones, such as cumambrin B (**3**) and ambrosin (**4**), belonging to the Guaianolide and Pseudoguaianolide families respectively.[3] One major problem associated with synthetic work in this area is control of the relative stereochemistry at the four contiguous positions, C-8a, -3a, -4, and -5. [*cf.* (**1**)]. Furthermore, any



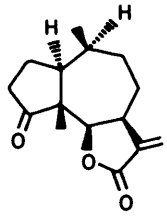
(**1**)



(**2**)

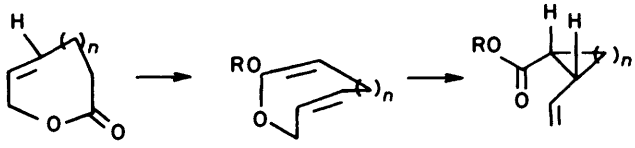


(**3**)



(**4**)

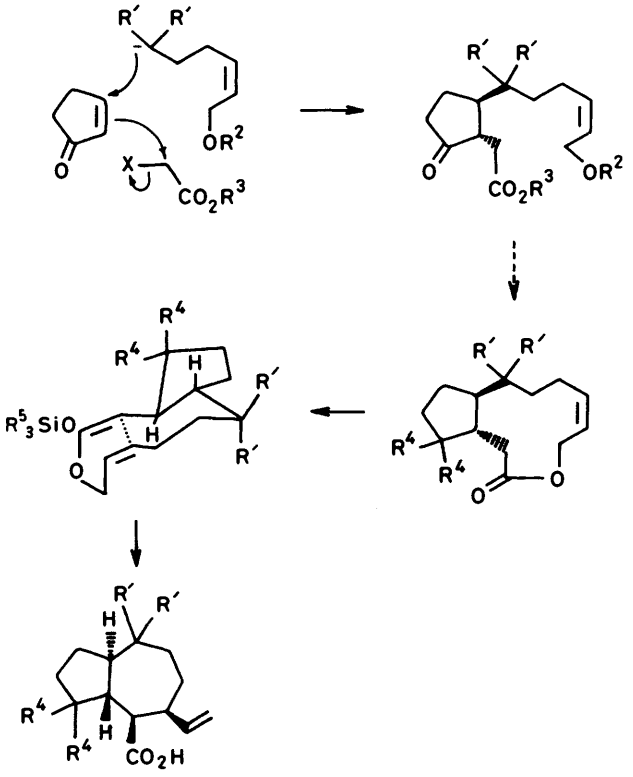
potentially general approach should aim to have appropriate functionality present at C-3 and C-8 to allow for independent manipulation of these two centres. We were attracted by the possibility of using an alicyclic Claisen rearrangement[4] [(**5**) ⟶ (**6**) ⟶ (**7**)] both to construct the seven-membered ring pre-



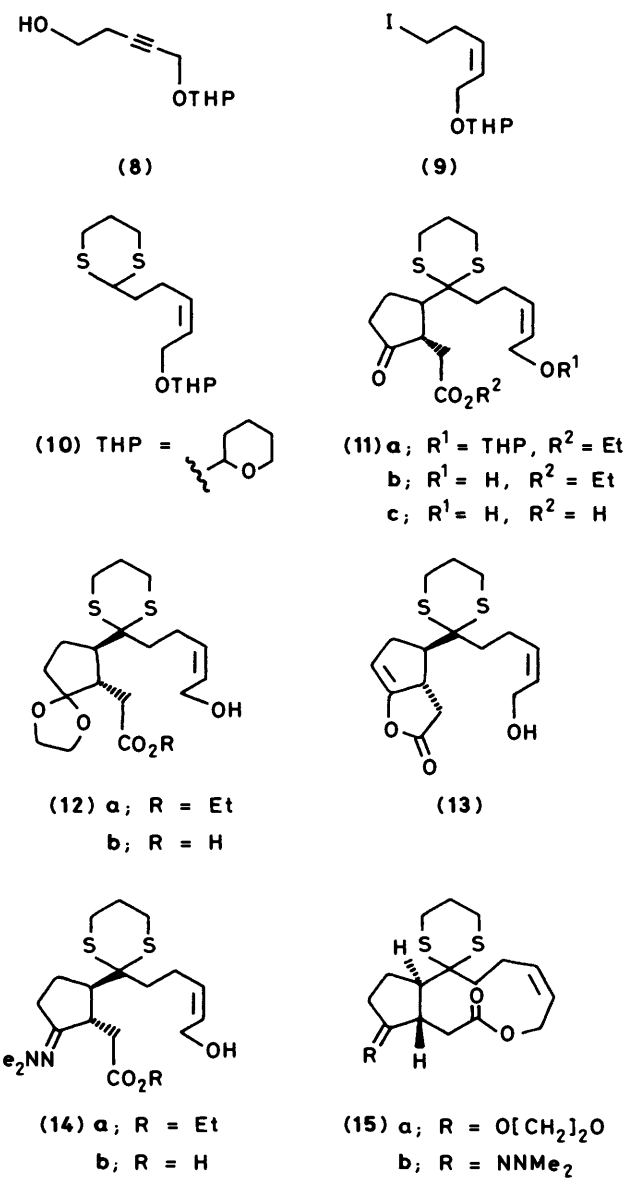
(**5**) (**6**) (**7**)

sent in the dictyols and to provide substituents at C-4 and C-5 with the required *cis* relative stereochemistry. Recent studies of this version of the Ireland–Claisen rearrangement[5] in which lactone rather than ester *O*-silyl enolates are used, have shown that for small and medium-sized unsubstituted lactones [(**5**); $n < 5$] the reactions proceed *via* a boat-like transition state (**6**) to give exclusively the *cis*-isomers (**7**). Furthermore, substituents around the lactone ring are most likely to adopt equatorial positions if possible. In the specific cases of precursors to the dictyols, a cyclopentane residue fused to the lactone ring with a *trans* stereochemistry would be expected to adopt such an equatorial position in the transition state, thereby delivering a product with the correct relative stereochemistries at all four contiguous centres (Scheme 1). As the *trans* relationship about the cyclopentane ring could be readily obtained by a conjugate addition–trapping sequence, which would also allow for the incorporation of appropriate functionality at the eventual C-3 and C-8 positions of the dictyol precursors, the approach outlined in Scheme 1 appeared to offer the attractions of relative brevity, stereoselectivity, and some generality. The successful realisation of these ideas is detailed below and suggests that such alicyclic Claisen rearrangements could find many other applications in this and other areas.

We decide to use a lithiated 1,3-dithiane to initiate the conjugate addition–trapping sequence and therefore we required the 2-substituted dithiane (**10**). This was obtained on large scale in four steps from the pent-2-yne-1,5-diol derivative (**8**). This starting material is easily obtained by condensation between the tetrahydropyranyl ether of prop-2-ynyl alcohol and ethylene oxide, using lithamide in liquid ammonia.[6] We found that the yield of the acetylene (**8**) was considerably improved if the ethylene oxide was first dried over calcium hydride then distilled into the reaction mixture containing the lithium acetylide. Subsequent Lindlar reduction, tosylation, and toluenesulphonate–iodide exchange proceeded uneventfully to give the *Z*-5-iodopentenol derivative (**9**) in excellent yield. This relatively unstable iodide was immediately used to alkylate 2-lithio-1,3-dithiane to give the key side-chain fragment (**10**).



Scheme 1.



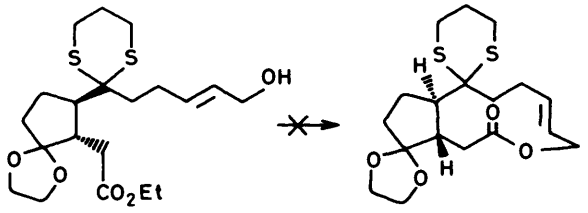
(8) (9) (10) THP = (11) a; R^1 = THP, R^2 = Et; b; R^1 = H, R^2 = Et; c; R^1 = H, R^2 = H (12) a; R = Et; b; R = H (13) (14) a; R = Et; b; R = H (15) a; R = O[CH_2]$_2$O; b; R = $NNMe_2$

Conjugate addition of the 2-lithio derivative of dithiane (**10**) to cyclopent-2-enone was effected by carrying out the reaction in the presence of hexamethylphosphoramide (HMPA) as described by Brown and Yamaichi.[7] The resulting ketone enolate was best trapped *in situ* using ethyl iodoacetate, to give the required disubstituted cyclopentanone (**11a**) in 65% isolated yield. The overall return was slightly lower (5—10%) both when methyl bromoacetate was used as trapping agent and also when 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one(DMPU)[8] was used in place of the toxic HMPA to direct the initial conjugate addition. Deprotection of the tetrahydropyranyl ether (**11a**) proceeded smoothly using toluene-*p*-sulphonic acid (PTSA) in ethanol to give the alcohol (**11b**); subsequent protection of the ketone function as the dioxolane derivative (**12a**) was then effected using standard conditions [$(CH_2OH)_2$, PTSA, C_6H_6]. The direct conversion of ketone (**11a**) into the dioxolane (**12a**) could also be accomplished using ethylene glycol and PTSA in benzene at reflux, although the yield tended to be lower than in the two-step procedure. We then simply needed to hydrolyse the ester group in the protected cyclopentanone (**12a**) to give the hydroxy acid (**12b**) prior to formation of the key macrolide (**15a**). While the ester group was readily hydrolysed using aqueous ethanolic potassium hydroxide, all attempts to liberate the free acid (**12b**), even under very carefully controlled conditions, resulted in concomitant loss of the dioxolane protecting group to give only the keto acid (**11c**). Presumably, the close proximity of the carboxylic acid and dioxolane functions allows intramolecular protonation of the latter by the former to occur during acidification, leading to rapid loss of the protecting group. Not unexpectedly, attempts to reprotect the ketone group of the hydroxy acid (**11c**) as the dioxolane derivative were unsuccessful. When we tried to lactonise directly the unprotected hydroxy acid (**11c**) using 2-chloro-1-methylpyridinium iodide[9] as coupling reagent, the only product was the five-membered enol lactone (**13**), again reflecting the proximity of the ketone and carboxylic acid functions in these compounds.

We therefore sought a more stable ketone-protecting group, and to this end found that the dimethylhydrazone derivative (**14a**) could be readily obtained from keto ester (**11b**) simply by heating the latter with 1,1-dimethylhydrazine. However, the ester group of the hydrazone (**14a**) proved surprisingly resistant to hydrolysis and a satisfactory yield of the required hydroxy acid (**14b**) was not realised. We were therefore forced to consider using hydroxy esters [(**12a**) and (**14a**)] as the immediate precursors of the required macrolides. In principle, such lactonisations should be possible by first forming an alkoxide derivative of the alcohol function which could then attack the ester group intramolecularly with displacement of ethoxide, given that high-dilution conditions are employed. We were relieved to discover that this was indeed possible; of a number of conditions tried, the best was found to be formation of the corresponding lithium alkoxides of esters (**12a**) or (**14a**), using n-butyl-lithium at *ca.* −40 °C, followed by heating these derivatives in dilute solution in tetrahydrofuran (THF) containing a trace of HMPA. In this way, the required macrolides [(**15a**) and (**15b**)] were obtained in 52 and 45%

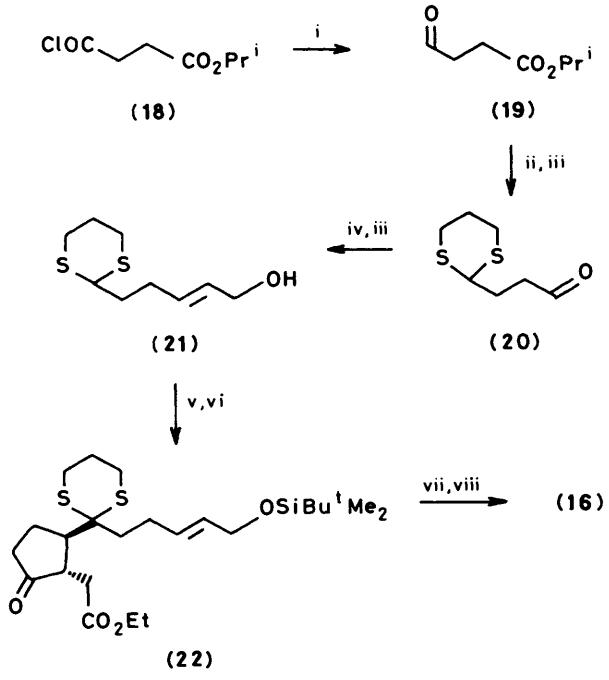
isolated yield, respectively. Interestingly, Vedejs and Larsen[10] have recently used the reverse of this approach to form the macrolide linkage in the necine alkaloid dilactones fulvine and crispatine. In these examples intramolecular coupling of a carboxylate anion, generated from the corresponding β-trimethylsilylethyl ester using tetra-n-butylammonium flouride, with a methanesulphonate gave the required 11-membered dilactones in high yield.

Throughout the work described above, t.l.c. and spectroscopic analysis showed that all compounds were stereochemically homogeneous. During the dioxolane-formation step [(**11b**) ⟶ (**12a**)], a small amount (< 10%) of the corresponding (*E*)-isomer (**16**) was also isolated. Although this could be



(**16**) (**17**)

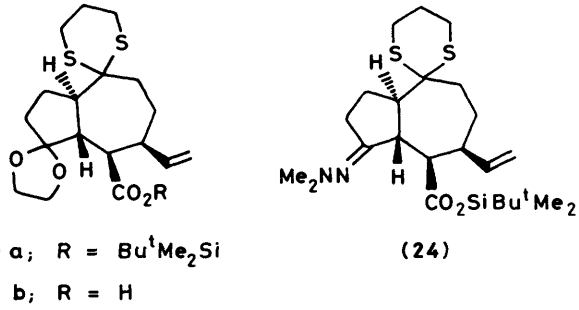
separated by careful column chromatography from the (*Z*)-isomer (**12a**), this was not necessary as parallel studies revealed that the (*E*)-macrolide (**17**) could not be obtained from hydroxy ester (**16**) using the method described above, or under a variety of related conditions [lactone (**15a**) and alcohol (**16**) were easily separated by column chromatography]. A larger sample of ester (**16**) was obtained by the route outlined in Scheme 2. Thus, Rosenmund reduction[11] of the acid chloride (**18**), readily obtained from succinic anhydride by sequential treatment with isopropyl alcohol and thionyl chloride, provided the aldehyde



Scheme 2. *Reagents and conditions*: i, 10% Pd–C, H_2, 2,6-lutidine, THF; ii, $HS[CH_2]_3SH$, $BF_3{\cdot}Et_2O$, $CHCl_3$; iii, Bu^i_2AlH, toluene, −70 °C; iv, $Ph_3P{=}CHCO_2Et$, $CHCl_3$, 20 °C; v, Bu^tMe_2SiCl, Et_3N, DMAP, C_6H_6, 20 °C; vi, as for (**10**) ⟶ (**11a**); vii, HF, H_2O, THF, 20 °C; viii, as for (**11b**) ⟶ (**12a**)

(**19**)[11] which was then converted into the dithiane derivative and reduced to the protected succinic dialdehyde (**20**).[12] Wittig homologation followed by reduction provided the (*E*)-alcohol (**21**), which was protected as the dimethyl-t-butylsilyl derivative; subsequent application of the conjugate addition–trapping sequence used for the preparation of compound (**11a**) then gave the cyclopentanone (**22**). Finally, conversion into hydroxy ester (**16**) was achieved by desilylation and ketalisation.

The crucial alicyclic Claisen rearrangements of the macrolides (**15a**) and (**15b**) were carried out by conversion of these into the corresponding *O*-silyl enolates, using $LiNPr^i_2$ (LDA) in THF and dimethyl-t-butylsilyl chloride at −78 °C, followed by heating the resulting solutions directly without isolation of the intermediate silyl enolates. T.l.c. analysis showed that the rearrangements were complete after *ca.* 10 min at reflux. In the case of lactone (**15a**), a simple aqueous work-up followed by chromatography and crystallisation gave the perhydroazulene (**23a**) as prisms, in 77% yield. Brief treatment with aqueous hydrogen fluoride then gave the corresponding acid (**23b**). The hydrazone derivative (**24**) was isolated in lower yield



(**23**) a; R = Bu^tMe_2Si (**24**)
b; R = H

(35%); although not rigorously proven, the indications were that this lower recovery was due to competitive metallation and *C*-silylation at the sites adjacent to the hydrazone function. Spectral data, especially ^1H and ^{13}C n.m.r., showed that each product [(**23a**) and (**24**)] was a single isomer with the same relative stereochemistry about the four contiguous centres at positions 3a, 4, 5, and 8a. While the observed coupling constants [$J_{3a,4}$ 9.6, $J_{3a,8a}$ 9.5, and $J_{4,5}$ 7.8 Hz] were consistent with the proposed structures, these did not provide definite proof and therefore an *X*-ray crystallographic determination was used to confirm the overall structure and detailed stereochemistry of the hydrazone derivative (**24**),[13] and hence of the corresponding dioxolane (**23a**).

This relatively brief route therefore provides the useful precursors [(**23a**) and (**24**)] of the dictyols in a stereospecific manner, presumably *via* a boat-like transition-state conformation as outlined in Scheme 1. Furthermore, the different carbonyl-protecting groups at C-3 and C-8 in these precursors will allow for independent manipulation of these sites. This work serves to emphasise the utility of the alicyclic Claisen rearrangement in the stereocontrolled synthesis of carbocyclic systems, and suggests that many other applications should be forthcoming.

Experimental

For general details, see A. G. Cameron and D. W. Knight, *J. Chem. Soc., Perkin Trans. 1*, 1986, 161. Throughout, the silica gel used was Merck grade 7736. Light petroleum refers to the fraction boiling in the range 60—80 °C.

2-[(*Z*)-5′-(*Tetrahydropyran-2-yloxy*)*pent*-3′-*enyl*]-1,3-*dithiane* (**10**).—Condensation of 3-(tetrahydropyran-2-yloxy)-prop-1-yne (113.75 g, 0.8 mol) with ethylene oxide (100 ml)

according to the procedure of Raphael and Roxburgh[6] gave 5-(tetrahydropyran-2-yloxy)pent-3-yn-1-ol (**8**) (90.3 g, 61%), b.p. 102—106 °C at 0.05 mmHg (lit.,[14] 116—120 °C at 0.7 mmHg). Yields were higher in this reaction if the ethylene oxide was first cooled to *ca.* −40 °C and dried over calcium hydride until effervescence ceased, then distilled directly into the reaction mixture.

A solution of the foregoing alcohol (90 g) in methanol (1 l) containing Lindlar catalyst (0.5 g; Fluka) was stirred vigorously under hydrogen. Gas uptake was rapid and intermittent cooling was necessary to keep the temperature at *ca.* 20 °C. After the required amount of hydrogen had been absorbed, the rate of reaction dropped markedly; the mixture was then filtered through diatomite and evaporated. Distillation of the residue gave (*Z*)-5-(tetrahydropyran-2-yloxy)pent-3-en-1-ol (88.4 g), b.p. 86—88 °C at 0.05 mmHg (lit.,[14] 94—96 °C at 0.35 mmHg); δ_H 1.38—1.95 (6 H, m), 2.37 (2 H, q, *J* 7 Hz, 2-H_2), 3.03 (1 H, OH), 3.64 (2 H, t, *J* 7 Hz, 1-H_2), 3.40—4.05 (2 H, m), 4.20 (2 H, dd, *J ca.* 7 and 6 Hz, 5-H_2), 4.58—4.74 (1 H, m), and 5.51—5.92 (2 H, m, 3- and 4-H).

A solution of the foregoing alcohol (88.4 g) in ice-cold pyridine (1 l) was treated with toluene-*p*-sulphonyl chloride (100 g). After 16 h at 0 °C, the mixture was worked up in the usual way to give the corresponding tosyl derivative (150.2 g) as a pale yellow oil, δ_H 1.38—1.98 (6 H, m), 2.48 (3 H, MeC_6H_4), 2.51 (partly obscured, 2 H, 2-H_2), 3.38—3.98 (2 H, m), 4.08 (2 H, t, *J* 7 Hz, 1-H_2), *ca.* 4.16 (partly obscured, 2 H, 5-H_2), 4.60—4.73 (1 H, m), 5.38—5.90 (2 H, m, 3- and 4-H), 7.43 (2 H, d, *J* 8 Hz) and 7.91 (2 H, d, *J* 8 Hz) (together ArH).

The crude tosyl derivative (150.2 g) was immediately dissolved in dry acetone (2 l), and sodium iodide (286 g) was added. The mixture was stirred at ambient temperature in the dark for 5 h, then evaporated. The resulting brown paste was partitioned between water (500 ml) and ether (500 ml). After separation, the aqueous layer was further extracted with ether (3 × 200 ml). The combined ether phases were washed with 1% aqueous sodium thiosulphate until colourless, followed by brine, then dried and evaporated to give (*Z*)-5-iodo-1-(tetrahydropyran-2-yloxy)pent-2-ene (**9**)[14] (137.3 g) as a yellow oil which darkened rapidly. Attempted vacuum distillation resulted in extensive loss, and so the material was used directly in the next step. The sample was pure according to both t.l.c. and ^{1}H n.m.r. spectroscopy, δ_H 1.39—2.00 (6 H, m), 2.70 (2 H, approx. q, *J* 7 Hz, 4-H_2), 3.19 (2 H, t, *J* 7 Hz, 5-H_2), 3.40—4.02 (2 H, m), 4.18 (2 H, dd, *J* 7 and 6 Hz, 1-H_2), 4.60—4.72 (1 H, m), and 5.43—5.92 (2 H, m, 2- and 3-H).

n-Butyl-lithium (283 ml of 2.5M solution in hexane; 0.71 mol) was added dropwise to a stirred solution of 1,3-dithiane (85 g, 0.71 mol) in THF (1.5 l) maintained at −20 °C. After 1 h at this temperature, the solution was cooled to −78 °C (acetone–solid CO_2) and a solution of the foregoing iodide (137 g, 0.46 mol) in THF (200 ml) was added dropwise. After 1 h at −78 °C, the solution was stirred overnight without further addition of coolant, then quenched with water (20 ml) and evaporated. The residue was partitioned between water (100 ml) and ether (500 ml). After separation, the aqueous layer was extracted with ether (100 ml) and the combined organic solutions were washed successively with water (50 ml) and brine (50 ml), then dried and evaporated to leave a yellow oil (165 g). Excess of 1,3-dithiane was removed by heating the sample at 60 °C (oil-bath) at 0.01 mmHg. Attempted distillation of the residue resulted in loss of the tetrahydropyranyl group and polymerisation; however, a small sample (0.5 g) was successfully subjected to Kugelrohr distillation and showed b.p. 158 °C (oven temp.) at 0.05 mmHg. Chromatography of a sample (30 g) of the product, after removal of an excess of 1,3-dithiane, over 70—230 mesh silica gel (400 g) eluted with 5% ethyl acetate in light petroleum (2 l) followed by 10% ethyl acetate in light petroleum gave the *title compound* (**10**) (16.3 g, 76%) as an oil, δ_H 1.38—2.46 (12 H, m), 2.79—2.96 (4 H, m, 2 × CH_2S), 3.38—4.00 (2 H, m), 4.05 (1 H, t, *J* 7 Hz, SCHS), 4.20 (2 H, dd, *J* 7 and 6 Hz, 5′-H_2), 4.59—4.72 (1 H, m), and 5.41—5.82 (2 H, m, 3′- and 4′-H); δ_C 19.55 (t), 24.73 (t), 25.55 (t), 26.08 (t), 30.26 (t), 30.76 (t), 35.25 (t), 46.75 (d, SCHS), 62.19 (t, CH_2O), 62.84 (t, CH_2O), 98.04 (d, OCHO), 127.68 (d, =CH), and 131.42 (d, =CH) (Found: C, 58.1; H, 8.6. $C_{14}H_{24}O_2S_2$ requires C, 58.3; H, 8.3%). The material was isomerically pure according to the ^{13}C n.m.r. data.

Ethyl t-2-[2-(Z)-(5-*Hydroxypent*-3-*enyl*)-1,3-*dithian*-2-*yl*]-5-*oxocyclopentan*-r-1-*ylacetate* (**11b**).—n-Butyl-lithium (18.3 ml of 1.6M solution in hexane; 29.3 mmol) was added dropwise to a stirred solution of 2-[(*Z*)-5-(tetrahydropyran-2-yloxy)pent-3-enyl]-1,3-dithiane (**10**) (7.9 g, 27.4 mmol) in THF (50 ml) maintained at −20 °C. After 1 h at −20 °C, the resulting red solution was cooled to −78 °C and treated with HMPA (5.13 ml, 29.4 mmol). After 20 min, cyclopent-2-enone (2.34 ml, 29.4 mmol) was added dropwise during 0.25 h. After a further 0.25 h, the solution was lemon yellow in colour. Ethyl iodoacetate (3.3 ml, 29 mmol) was added in one portion and, after a further 0.5 h at −78 °C, the solution was warmed to room temperature during 1 h, then poured into water (100 ml), and extracted with ether (5 × 50 ml). The combined extracts were washed with brine (50 ml), shaken with sodium chloride (20 g), then dried and evaporated. The residue was chromatographed using silica gel eluted with 20% ethyl acetate in light petroleum to give, after elution of a small amount of ethyl iodoacetate, the starting dithiane (0.95 g) followed by the *tetrahydropyranyl ether* (**11a**) (7.15 g, 57%, or 65% based on recovered starting material) as an oil, $\nu_{max.}$(film) 1 732 cm^{-1}; δ_H 1.25 (3 H, t, *J* 7 Hz, OCH_2Me), 1.40—1.78 (6 H, m), 1.80—2.57 (10 H, m), 2.68—2.98 (6 H, m), 3.02—3.12 (2 H, m), 3.38—3.98 (2 H, m), 4.14 (2 H, q, *J* 7 Hz, OCH_2Me), 4.20 (2 H, dd, *J* 7 and 6 Hz, CH_2OTHP), 4.62—4.72 (1 H, m, OCHO), and 5.58—5.75 (2 H, m, CH=CH) (Found: C, 60.6; H, 8.0. $C_{23}H_{36}O_5S_2$ requires C, 60.5; H, 7.9%). The compound was homogeneous according to t.l.c. The intermediate ketone enolate could also be alkylated by methyl bromoacetate to give the corresponding methyl ester in slightly lower yield (*ca.* 5%).

A solution of the foregoing tetrahydropyranyl ether (3.1 g) in ethanol (25 ml) containing PTSA monohydrate (0.15 g) was stirred at ambient temperature until t.l.c. indicated disappearance of the ether (*ca.* 3 h). The solvent was then evaporated and the residue was partitioned between saturated aqueous sodium hydrogen carbonate (50 ml) and ether (50 ml). The aqueous layer was extracted with fresh ether (2 × 25 ml) and the combined ether phases were washed successively with water (10 ml) and brine (10 ml), then dried and evaporated to leave the *alcohol* (**11b**) (2.47 g, 94%) as an oil, $\nu_{max.}$(film) 3 430 and 1 730 cm^{-1}; δ_H 1.25 (3 H, t, *J* 7 Hz, OCH_2Me), 1.80—2.55 (10 H, m), 2.69—3.00 (6 H, m), 3.02—3.15 (2 H, m), 4.16 (2 H, q, *J* 7 Hz, OCH_2Me), 4.24 (2 H, d, *J* 6 Hz, CH_2OH), and 5.54—5.84 (2 H, m, CH=CH) (Found: C, 58.3; H, 7.7. $C_{18}H_{28}O_4S_2$ requires C, 58.1; H, 7.5%).

Ethyl 2-*Ethylenedioxy*-t-5-[2-(*Z*)-(5-*hydroxypent*-3-*enyl*)-1,3-*dithian*-2-*yl*]*cyclopentan*-r-1-*ylacetate* (**12a**).—A solution of the foregoing hydroxy keto ester (**11b**) (2.15 g, 5.8 mmol) and dry ethylene glycol (5 ml) in dry benzene (100 ml) containing PTSA (0.2 g) was refluxed under a Dean and Stark water separator for 4.75 h. During the later stage of the reaction, last traces of water were removed by filling the separator with freshly activated 3A molecular sieves. The cooled solution was poured into dil. aqueous sodium hydrogen carbonate (100 ml) and the layers were separated. The aqueous layer was extracted with benzene (3 × 50 ml) and the combined organic solutions washed successively with saturated aqueous sodium hydrogen

carbonate (10 ml), water (3 × 50 ml), and brine (50 ml), then dried and evaporated. Chromatography of the residue using silica gel eluted with 40% ethyl acetate–n-hexane containing a trace of triethylamine gave the *dioxolane* (**12a**) (1.92 g, 80%) as an oil, $\nu_{max.}$(film) 3 340 and 1 730 cm^{-1}; δ_H (250 MHz) 1.28 (3 H, t, *J* 7 Hz, OCH_2Me), 1.73 (1 H, br s, OH), 1.84—2.48 (10 H, m), 2.67—3.03 (6 H, m), 3.05—3.13 (2 H, m), 3.67 (4 H, OCH_2CH_2O), 4.20 (2 H, q, *J* 7 Hz, OCH_2Me), 4.22 (2 H, d, *J* 6.15 Hz, CH_2OH) and 5.51—5.75 (2 H, m, CH=CH); δ_C 13.90 (OCH_2Me), 23.00 (CH_2), 23.56 (CH_2), 24.73 (CH_2), 25.65 (2 × CH_2), 34.64 (CH_2), 35.50 (CH_2), 37.50 (CH_2), 46.29 (CH), 48.28 (CH), 59.96 (SCS), 58.11 (OCH_2), 59.90 (OCH_2), 63.87 (OCH_2), 64.81 (OCH_2), 116.84 (OCO), 129.28 (=CH), 131.28 (=CH), and 172.85 (C=O); *m/z* 416 (M^+, 5%, $C_{20}H_{32}O_5S_2$), 398 (5, $C_{20}H_{30}O_4S_2$, $M - H_2O$), 331 (11, $C_{15}H_{23}O_4S_2$, loss of pentenyl side-chain), 287 (15, $C_{13}H_{19}O_3S_2$), 203 [100, $C_9H_{15}OS_2$, pentenyl-dithiane (side-chain)], 199 (31, $C_9H_{11}OS_2$, loss of pentenyl and acetic ester side-chains), and 99 (21, $C_5H_7O_2$) (Found: C, 57.6; H, 8.0. $C_{20}H_{32}O_5S_2$ requires C, 57.7; H, 7.7%). The material was isomerically pure according to t.l.c. and the above data, especially the ^{13}C n.m.r. spectrum.

Tetrahydropyranyl ether (**11a**) could also be directly converted into the dioxolane (**12a**) by the above procedure, but yields were slightly lower and the product contained *ca.* 20% of the corresponding dioxolane-THP ether.

Ethyl 2-Dimethylhydrazino-t-5-[2-(Z)-(5-*hydroxypent*-3-*enyl*)-1,3-*dithian*-2-*yl*]*cyclopentan*-r-1-*ylacetate* (**14a**).—A solution of the hydroxy keto ester (**11b**) (1.1 g, 3 mmol) in freshly distilled 1,1-dimethylhydrazine (5 ml) was refluxed for 24 h, then evaporated. Chromatography of the residue using silica gel eluted with 70% ethyl acetate–hexane gave the *hydrazone* (**14a**) (1.0 g, 82%) as an oil, $\nu_{max.}$(film) 3 380, 1 730, and 1 650 cm^{-1}; δ_H 1.27 (3 H, t, *J* 7 Hz, OCH_2Me), 1.80—3.35 (18—19 H, m), 2.49 (6 H, NMe_2), 4.16 (2 H, q, *J* 7 Hz, OCH_2Me), 4.24 (2 H, d, *J* 6 Hz, CH_2OH), and 5.39—5.84 (2 H, m, CH=CH) (Found: C, 57.7; H, 8.6. $C_{20}H_{34}N_2O_3S_2$ requires C, 58.0; H, 8.2%).

(Z)-12-*Ethylenedioxy*-1,4,7,8,9,r-9a,10,11,12,t-12a-*decahydro*-9-*trimethylenedithio*-2H-*cyclopent*[d]*oxaundecin*-2-*one* (**15a**).—A solution of n-butyl-lithium (0.85 ml of 1.6M solution in hexane; 1.36 mmol) in hexane (4 ml) was added during 5 min to a stirred solution of the foregoing hydroxy ester (**12a**) (0.55 g, 1.32 mmol) and HMPA (2 ml) in THF (800 ml) maintained at *ca.* −40 °C. The resulting yellow solution was refluxed for 20 h, then cooled and evaporated. The residue was partitioned between ether (100 ml) and water (50 ml); after separation of the organic layer, the aqueous layer was extracted with fresh ether (2 × 30 ml) and the combined ether solutions were washed successively with water (3 × 20 ml) and brine (20 ml), then dried and evaporated. Chromatography of the residue using silica gel eluted with 20% ethyl acetate in light petroleum gave a pale yellow solid which, on crystallisation from ether–light petroleum, afforded the *lactone* (**15a**) (0.255 g, 52%) as small prisms, m.p. 146—147 °C; $\nu_{max.}$($CHCl_3$) 1 735 cm^{-1}, δ_H (250 MHz) 1.56 (1 H, t, *J* 12.3 Hz), 1.68—2.00 (6 H, m), 2.02—2.14 (1 H, m), 2.19 (1 H, dd, *J* 13.3 and 11.9 Hz, CHC=O), 2.29 (1 H, ddt, *J* 12.9, 11.0, and 7.4 Hz), 2.42—2.88 (7 H, m), 3.02 (1 H, ddd, *J* 14.3, 12.9, and 2.8 Hz), 3.86—4.04 (4 H, m, OCH_2CH_2O), 4.65 (1 H, ddd, *J* 15.5, 4.1, and 2.4 Hz, OCH_AH_B), 4.87 (1 H, ddd, *J* 15.5, 4.4, and *ca.* 0.7 Hz, OCH_AH_B), 5.42 (1 H, ddd, *J* 11.6, 4.4, and 4.1 Hz, 5-H), and 5.55—5.72 (1 H, m, 6-H); δ_C 24.39 (t), 25.15 (t), 25.19 (t), 25.59 (t), 25.65 (t), 34.12 (t), 36.34 (t), 38.97 (t), 42.41 (d, ring junction CH), 49.69 (d, ring junction CH), 58.55 (s, C-9), 63.16 (t, OCH_2), 63.87 (t, OCH_2), 64.59 (t, OCH_2), 116.89 (s, C-12), 123.64 (d, =CH), 129.89 (d, =CH), and 173.23 (s, C-2); *m/z* 370 (M^+, 35%, $C_{18}H_{26}O_4S_2$), 296 (18, $C_{15}H_{20}O_4S$, $M - C_3H_6S$), 263 (8, $C_{15}H_{19}O_4$, $M - C_3H_7S_2$), 184 (34, $C_9H_{12}S_2$), 132 (50, $C_5H_8S_2$, dithiane–CH_2), 106 (24, $C_3H_6S_2$), 99 (100, $C_5H_7O_2$), and 86 (42, $C_4H_6O_2$) (Found: C, 58.2; H, 7.0. $C_{18}H_{26}O_4S_2$ requires C, 58.4; H, 7.0%).

A related method also gave the lactone, but in lower yields. Thus, treatment of the hydroxy ester (**12a**) (4.16 g, 10 mmol) in benzene (1.5 l) and HMPA (4 ml) with lithium ethoxide (2 mmol) at room temperature for 5 min, followed by reflux for 24 h with continual slow removal of the solvent (final volume *ca.* 500 ml), followed by work-up as described above, gave the lactone (**15a**) in 44% yield (1.62 g).

(Z)-12-*Dimethylhydrazono*-1,4,7,8,9,r-9a,10,11,12,t-12a-*decahydro*-9-*trimethylenedithio*-2H-*cyclopent*[d]*oxaundecin*-2-*one* (**15b**).—Lactonisation of the hydroxy ester hydrazone (**14a**) (1.13 g) by the above procedure, using n-BuLi–THF–HMPA, gave the *lactone* (**15b**) (0.45 g, 45%), after chromatography over silica gel eluted with 50% ethyl acetate–light petroleum, as a pale yellow oil, $\nu_{max.}$(film) 1 735 cm^{-1}; δ_H 1.8—3.35 (18 H, m), 2.50 (6 H, NMe_2), 4.23 (1 H, dd, *J* 14 and 6 Hz, OCH_AH_B), 5.18 (1 H, br dt, *J* 14 and *ca.* 3 Hz, OCH_AH_B), and 5.60—6.12 (2 H, m, CH=CH); δ_C 24.41, 25.05, 25.47, 25.53, 25.90, 28.68, 36.00, 40.79 (all CH_2), 42.91 (CH), 46.74 (2 × CH_3N), 47.64 (CH), 58.73 (C-9), 60.64 (CH_2O), 122.77 (=CH), 135.49 (=CH), 171.00 (C-2), and 175.11 (C-12); *m/z* 368 (M^+, 99%, $C_{18}H_{28}N_2O_2S_2$), 335 (9, $C_{18}H_{27}N_2O_2S$, M − SH), 293 (76, $C_{15}H_{21}N_2O_2S$, $M - C_3H_7S$), 261 (71, $C_{15}H_{21}N_2O_2S$, $M - C_3H_7S_2$), 165 (33, $C_9H_{13}N_2O$, $M - S[CH_2]_3SC[CH_2]_2CH{=}CHCH_2OH$), and 132 (100, $C_5H_8S_2$) (Found: C, 58.5; H, 7.5. $C_{18}H_{28}N_2O_2S_2$ requires C, 58.7; H, 7.6%).

3-*Ethylenedioxy*-1,2,3,c-3a,4,5,6,7,8,t-8a-*decahydro*-8-*trimethylenedithio*-c-5-*vinylazulene*-r-4-*carboxylic Acid* (**23b**), *and the Corresponding Dimethyl-t-butylsilyl Ester* (**23a**).—A solution of the dioxolane lactone (**15a**) (0.5 g, 1.35 mmol) in THF (6 ml) was added dropwise during 10 min to a stirred solution of LDA [from di-isopropylamine (0.49 ml, 3.5 mmol) and n-butyl-lithium (2.13 ml of 1.6M solution in hexane; 3.4 mmol)] in THF (25 ml) at −78 °C. After 0.5 h at this temperature, a solution of dimethyl-t-butylsilyl chloride (0.522 g, 3.47 mmol) in THF (2 ml) was added. After a further 10 min at this temperature, the solution was heated to reflux during 5 min. After *ca.* 10 min at reflux, t.l.c. analysis indicated complete consumption of starting material. The solution was cooled and evaporated and the residue was partitioned between ether (50 ml) and water (50 ml). After separation, the aqueous layer was extracted with fresh ether (2 × 25 ml) and the combined ether solutions were washed with brine (10 ml), then dried and evaporated. Chromatography of the residue over silica gel eluted with 5% ethyl acetate–light petroleum gave the *perhydroazulene* (**23a**) (0.502 g, 77%) as prisms, m.p. 146 °C (from ether–n-hexane); $\nu_{max.}$(KBr) 1 704 and 1 618 cm^{-1}; δ_H (400 MHz) 0.24 (3 H, MeSi), 0.25 (3 H, MeSi), 0.92 (9 H, Me_3CSi), 1.47 (1 H, ddd, *J* 15.2, 6.8, and 2.6 Hz, 7-H), 1.66—1.71 (2 H, m, 1- + 2-H), 1.77—1.89 (3 H, m, 2-H + 6-H + $CH_AH_BCH_2S$), 2.06—2.13 (1 H, m, $CH_AH_BCH_2S$), 2.17 (1 H, ddt, *J* 12.0, 2.6, and 1.6 Hz, 6-H), 2.28 (1 H, dddd, *J* 10.5, 9.5, 5.2, and *ca.* 1 Hz, 8a-H), 2.35 (1 H, ddt, *J* 16.8, 8.0, and 55.2 Hz, 1-H), 2.43 (1 H, br app. q, *J* 7.8 Hz, 5-H), 2.60—2.67 (2 H, m, 2 × CHS), 2.79 (1 H, dd, *J* 9.6 and 7.8 Hz, 4-H), 2.90—3.06 (3 H, m, 7-H + 2 × CHS), 3.09 (1 H, br t, *J ca.* 9.5 Hz, 3a-H), 3.76—3.96 [4 H, m, $O(CH_2)_2$], 4.96 (1 H, ddd, *J* 10.4, 1.2, and 1.1 Hz, $CH{=}CH_cH_t$), 5.01 (1 H, dt, *J* 17.2 and 1.2 Hz, $CH{=}CH_cH_t$), and 5.74 (1 H, ddd, *J* 17.2, 10.4, and 8.0 Hz, $CH{=}CH_2$); δ_C −5.08 (MeSi), −4.82 (MeSi), 17.42 (CSi), 25.23 (C-1 + C-7), 25.46 (C-6), 25.54 (3 × Me), 26.03 (CH_2CH_2S), 26.65 (CH_2S), 34.57 (C-2), 42.91 (CH_2S), 45.29 (C-3a), 45.58 (C-5), 47.24 (C-8a), 47.85 (C-4), 59.12 (C-8), 64.62 (OCH_2), 64.78 (OCH_2), 113.82 (=CH_2), 117.52 (C-3), 140.72 (=CH), and 174.80 (C=O); *m/z* 484 (M^+, 100%, $C_{24}H_{40}O_4S_2Si$),

427 (53, $C_{20}H_{31}O_4S_2Si$, M − Bu^t), 377 (25, $C_{21}H_{33}O_4Si$, M − $C_3H_7S_2$), 277 (16, $C_{15}H_{21}O_3Si$), 173 [20, $C_{12}H_{13}O$(?)], 145 (35, $C_6H_9S_2$), 99 (82, $C_5H_7O_2$), 75 (83, C_3H_7S), and 73 (87, C_3H_9Si) (Found: C, 59.3; H, 8.3. $C_{24}H_{40}O_4S_2Si$ requires C, 59.5; H, 8.3%).

The foregoing silyl ester (**23a**) (0.102 g) was treated with a solution of 40% aqueous hydrofluoric acid (1 ml) in THF (5 ml). After 5 min at ambient temperature, t.l.c. indicated desilylation to be complete. The solution was diluted with water (50 ml) and extracted with dichloromethane (5 × 10 ml). The combined extracts were washed successively with water (2 × 10 ml) and brine (10 ml), then dried and evaporated. Crystallisation of the residue from ethyl acetate–n-hexane gave the *acid* (**23b**) (0.075 g, 98%) as a powder, m.p. 208—210 °C (decomp., with darkening at *ca.* 188 °C); $\nu_{max.}$(KBr) 1 704 cm^{-1}; δ_H (250 MHz) 1.49 (1 H, ddd, *J* 14.5, 5.5, and *ca.* 0.7 Hz, 7-H), 1.68—2.41 (9 H, m), 2.49 (1 H, app. q, *J* 8.2 Hz, 5-H), 2.66 (2 H, dt, *J* 14.5 and 3.6 Hz), 2.82 (1 H, dd, *J* 10.5 and 7.3 Hz, 4-H), 2.89—3.14 (4 H, m), 3.79—4.00 (4 H, m, OCH_2CH_2O), 4.98 (1 H, ddd, *J* 10.1, *ca.* 1.5 and 1 Hz, CH–CH_cH_t), 5.05 (1 H, ddd, *J* 17.1, 1.3, and *ca.* 0.9 Hz, CH=CH_cH_t), and 5.81 (1 H, ddd, *J* 17.1, 10.1, and 8.2 Hz, C*H*=CH_2) (Found: C, 58.5; H, 7.2. $C_{18}H_{26}O_4S_2$ requires C, 58.4; H, 7.0%).

Dimethyl-t-butylsilyl 3-*Dimethylhydrazono*-1,2,3,c-3a,4,5,6 7,8,t-8a-*decahydro*-8-*trimethylenedithio*-c-5-*vinylazulene*-r-4-*carboxylate* (**24**).—By the procedure detailed above, Claisen rearrangement of the lactone hydrazone (**15b**) (0.198 g, 0.54 mmol) followed by chromatography using silica gel eluted with 20% ethyl acetate in light petroleum gave the *perhydroazulene* (**24**) (0.093 g, 35%) as pale yellow prisms (from ether–pentane), m.p. 148—149 °C; $\nu_{max.}$(KBr) 1 706 and 1 620 cm^{-1}; δ_H (250 MHz) 0.28 (3 H, MeSi), 0.29 (3 H, MeSi), 0.93 (9 H, Me_3CSi), 1.51 (1 H, ddd, *J* 14.9, 5.4, and 0.8 Hz, 7-H), 1.76—1.88 (2 H, m), 2.08—2.32 (6 H, m), 2.43 (6 H, Me_2N), 2.48 (1 H, app. q, *J* 7.9 Hz, 5-H), 2.61—2.73 (4 H, m, including at δ 2.65, dd, *J* 9.5 and 7.5, 4-H), 2.92—3.10 (3 H, m), 3.51 (1 H, dt, *J* 9.5 and 1 Hz, 3a-H), 4.96 (1 H, ddd, *J* 10.1, *ca.* 1.5, and 1 Hz, CH=CH_cH_t), 5.02 (1 H, ddd, *J* 17.1, 1.3, and *ca.* 0.9 Hz, CH=CH_cH_t), and 5.77 (1 H, ddd, *J* 17.1, 10.1, and 7.9 Hz, C*H*=CH_2); *m/z* 482 (M^+, 15%, $C_{24}H_{42}N_2O_2S_2Si$), 425 (12, $C_{20}H_{33}N_2O_2S_2Si$, M − Bu^t), 323 (8, $C_{17}H_{27}N_2S_2$, M − $CO_2SiBu^tMe_2$), 296 (10, $C_{15}H_{28}N_2O_2Si$, cleavage at C8–8a and 4–5), 145 (7, $C_6H_9S_2$), 75 (100, C_3H_7S), and 73 (16, C_3H_9Si) (Found: C, 59.7; H, 9.0; N, 5.8. $C_{24}H_{42}N_2O_2S_2Si$ requires C, 59.8; H, 8.7; N, 5.8%).

Acknowledgements

We thank Mr. R. Fleming for help in obtaining the n.m.r. data, and the S.E.R.C. for financial support.

References

1 For a listing, see 'Dictionary of Organic Compounds,' 5th edn., Chapman and Hall, London, 1982.
2 N. Enoki, K. Tsuzuki, S. Omura, R. Ishida, and T. Matsumoto, *Chem. Lett.*, 1983, 1627; C. Pathirana and R. J. Andersen, *Can. J. Chem.*, 1984, **62**, 1666. See also M. Ishitsuka, J. Tanaka, M. Chihara, and H. Kakisawa, *Chem. Lett.*, 1985, 151; J. Tanaka and T. Higa, *ibid.*, p. 231, and references therein.
3 For a review see N. H. Fischer, E. J. Olivier, and H. D. Fischer, *Prog. Chem. Org. Nat. Prod.*, 1979, **38**, 47.
4 S. Danishefsky. R. L. Funk, and J. F. Kerwin, Jr., *J. Am. Chem. Soc.*, 1980, **102**, 6889; S. Danishefsky and K. Tsuzuki, *ibid.*, p. 6891; M. M. Abelman, R. L. Funk, and J. D. Munger, Jr., *ibid.*, 1982, **104**, 4030; A. G. Cameron and D. W. Knight, *Tetrahedron Lett.*, 1982, **23**, 5455; *J. Chem. Soc., Perkin Trans. 1*, 1986, 161; R. K. Brunner and H.-J. Borschberg, *Helv. Chim. Acta*, 1983, **66**, 2608; R. L. Funk and J. D. Munger, Jr., *J. Org. Chem.*, 1985, **50**, 707; A. G. Cameron and D. W. Knight, *Tetrahedron Lett.*, 1985, **26**, 3503.
5 R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, **94**, 5897; R. E. Ireland, R. H. Mueller, and A. K. Willard, *ibid.*, 1976, **98**, 2868.
6 R. A. Raphael and C. M. Roxburgh, *J. Chem. Soc.*, 1952, 3875.
7 C. A. Brown and A. Yamaichi, *J. Chem. Soc., Chem. Commun.*, 1979, 100.
8 T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385.
9 T. Mukaiyama, M. Usui, and K. Saigo, *Chem. Lett.*, 1976, 49.
10 E. Vedejs and S. D. Larsen, *J. Am. Chem. Soc.*, 1984, **106**, 3030. See also K. Narasaka, T. Sakakura, T. Uchimaru, and D. Güedin-Vuong, *ibid.*, p. 2954.
11 A. W. Burgstahler, L. O. Weigel, and G. C. Shaefer, *Synthesis*, 1976, 767.
12 *Cf.* A. Murai, M. Ono, and T. Masamune, *J. Chem. Soc., Chem. Commun.*, 1977, 573; S. D. Burke, T. H. Powner, and M. Kageyama, *Tetrahedron Lett.*, 1983, **24**, 4529.
13 M. J. Begley, A. G. Cameron, and D. W. Knight, *J. Chem. Soc., Chem. Commun.*, 1984, 827.
14 R. F. Borch, A. J. Evans, and J. J. Wade, *J. Am. Chem. Soc.*, 1977, **99**, 1612.

Received 19*th December* 1985; *Paper* 5/2237