Tetrahedron Vol. 35, pp. 2389 to 2396
Pergamon Press Ltd., 1979. Printed in Great Britain

SESQUITERPENE LACTONES

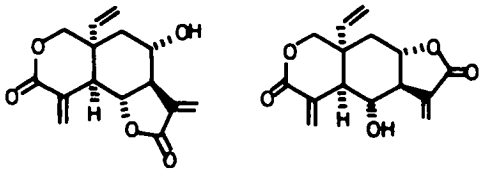
A TOTAL SYNTHESIS OF (±)-VERNOLEPIN

F. ZUTTERMAN, H. DE WILDE, R. MIJNGHEER, P. DE CLERCQ and M. VANDEWALLE*
State University of Ghent, Department of Organic Chemistry, Laboratory of Organic Synthesis, Krijgslaan, 271 (S.4), B-9000 Gent, Belgium

(*Received in UK 22 February 1979*)

Abstract—A novel synthesis of (±)-Vernolepin (1) is described. A suitably substituted *cis*-fused 2-oxa-3-decalone precursor (29) has been constructed starting from 2,5-cyclohexadiene carboxylic acid via an intramolecular cyclopropanation reaction (23 to 18). The route culminated in the synthesis of Grieco's lactone (53) which has previously been converted to (±)-vernolepin (1) and (±)-vernomenin (2).

Since its discovery,[1] together with its congener vernomenin (2), the elemanolide dilactone vernolepin (1) has been the subject of synthetic activity by numerous research groups.[2-11] So far only the groups of Grieco[2a] and of Danishefsky[4a] in 1976 and more recently the groups of Schlessinger[11b] and of Isobe[7] have terminated successfully their synthetic efforts.



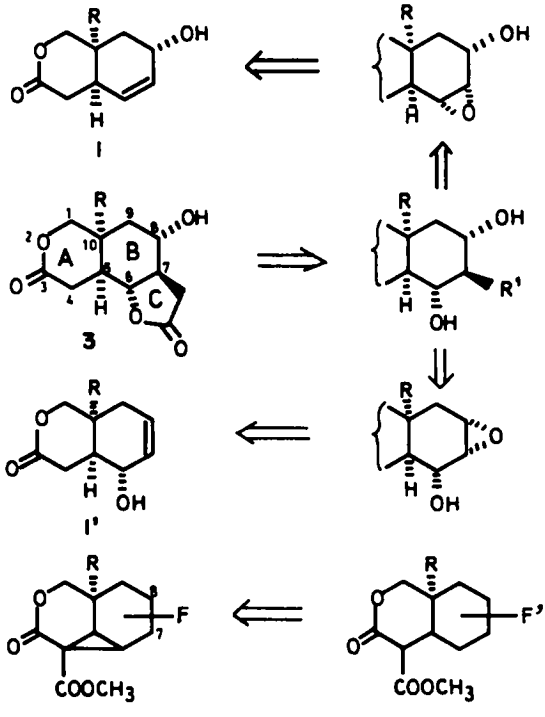
1 2

Scheme 1.

In the present paper we want to describe our own results in this area; the central idea of our approach, which consists of the formation of a suitably substituted *cis*-fused 2-oxa-3-decalone (AB rings) from a tricyclic precursor (ii) has been the subject of a preliminary publication.[8a] The all trans configuration of the homoallylic α-methylene-γ-lactone (ring C) moiety calls for a precursor molecule possessing an allylic alcohol functionality at the 6-, 7- and 8-positions. Indeed a classical approach is based on the trans-diaxial opening of a *cis*-hydroxy epoxide by an appropriate nucleophile R'; this method has also been adopted by Danishefsky[4a] and Schlessinger.[11b] A priori the two isomeric allylic alcohols are appropriate. Both suitably substituted *cis*-fused 2-oxa-3-decalone precursor molecules i and/or i' were therefore our primary targets; their synthesis can be performed along similar lines, involving an intramolecular carbenoid cyclopropanation reaction.

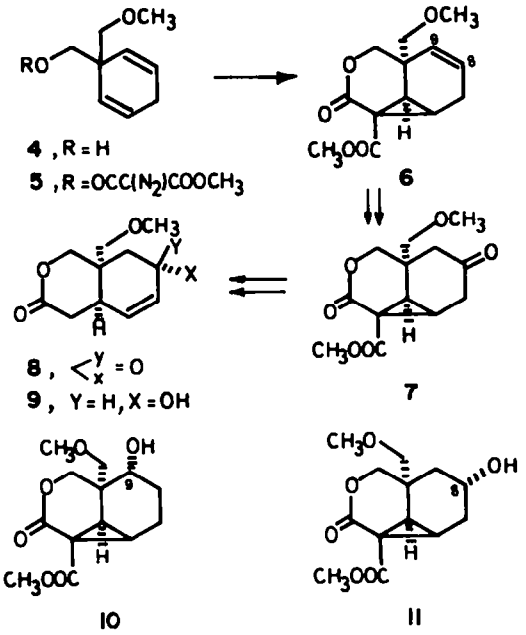
The choice of the functionality F (from which the allylic alcohol has to be constructed) and the mode of cyclopropane ring opening (ii→iii, inter- or intramolecular) is dictated by the particular approach to either i or i'. The projected route would then eventually lead to bisnorvernolepin (3; R = vinyl); it has indeed been shown originally by Grieco[2a] that preferential γ-lactone formation occurs with the 6-OH group and that both essential α-methylene units can be introduced simultaneously.

The first approach (Scheme 3) involving the intramolecular cyclopropane ring opening,[12] was directed towards the synthesis of the enone 8, a precursor of the allylic alcohol 9 (i). The ready availability of 1,1-disubstituted 2,5-cyclohexadienes[13] prompted us to choose 4 as the starting material and to test the cyclopropanation reaction on the symmetrical compound 5. The tricyclic product 6 would then be transformed to 7 and the latter by intramolecular ring opening to the enone 8. The synthesis of 6 (m.p. 112°), starting from 2,5-cyclohexadiene carboxylic acid using a five step sequence (overall yield 30%) has already been described.[8a] The planned transformation of 6 to 7, however, led to frustrating results. Attack of diborane from the convex side of 6 on the least hindered 8-position, followed by oxidative work-up was expected to yield the alcohol 11. However,



I 3 I' II III

Scheme 2.

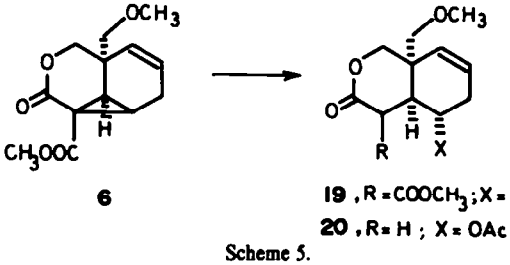


Scheme 3.

only the isomer **10** was obtained in low yield, probably resulting from directed hydroboration[2c] by the angular α-methoxymethyl group. The ^{1}H NMR spectral data for H-9 (triplet at 3.91 ppm; $^3J = 2.7$ Hz) are in accord with the axial orientation of the 9-OH group.

We then turned our attention to the bromohydrin addition product of **6** obtained in 87% yield by treatment with N-bromosuccinimide in water–dioxane. The shown stereochemistry for **12** would result from bromine attack from the convex side. At first inspection the spectroscopic data for the adduct were in agreement with the proposed structure **12**. The correct relative configuration at the 8- and 9-position was proven by the following revealing reaction. Our purpose was to oxidize **12** to the α-bromo ketone **13**. However, the remarkably slow Jones oxidation afforded (low yield) a single product spectroscopically identified as **14**. This result and the observation that the C-1 geminal protons (AB pattern) in the bromohydrin adduct resonate at higher field (3.44 and 3.60 ppm) than is the case for **10** (4.07 and 4.26 ppm) led us to reassign the structure as the cyclic ortho acid **15** and to envisage an equilibrium in solution between **15** and the lactones **12** and **12'**. Oxidation of the primary alcohol function in **12'** leads to the acid **16**, which due to the trans-diaxial position of the carboxyl group and the Br atom allows facile fragmentation to the olefin **14**. The intermediacy of **12'** in the proposed mechanism is strongly supported by the isolation of **17** (m.p. 111–113°; 67% yield) upon treatment of **15** with acetic anhydride in pyridine.

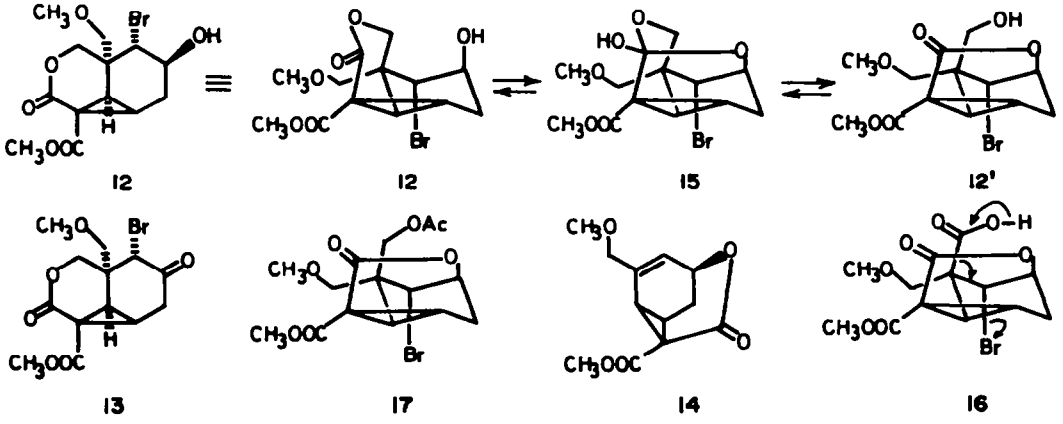
These results brought us to focus our attention to the intermolecular mode of cyclopropane ring opening (**ii** → **iii**); this reaction should provide a third chiral center on the B-ring with the desired stereochemistry. In order to correlate **iii** with our primary targets **i** and **i'** (Scheme 2), F must represent a double bond at the future 7,8-position. An obvious precursor is therefore tricyclic olefin **18** (Scheme 6); solvolysis would lead to **i'**, while reaction with thiophenolate anion and subsequent 2,3-sigmatropic rearrangement[14] of the corresponding sulfoxide allows access to **i**.



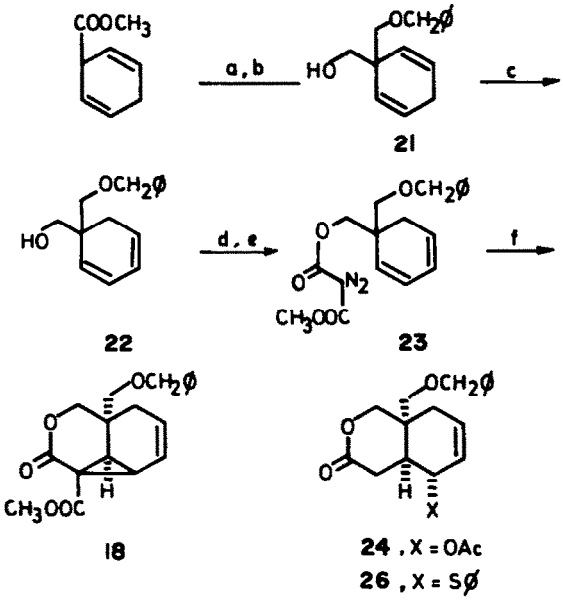
Scheme 5.

The possibilities for intermolecular cyclopropane ring opening were examined on **6** as a model compound for **18**; it was hopeful to observe that **6** could easily be converted to the 2-oxa-3-decalones **19** (m.p. 132–134°; yield 80%) using sodium thiophenolate in refluxing methanol (4 hr) and to **20** (70% yield) using acetic acid and a trace of sulphuric acid at 90° (3 hr).[8a]

The seven-step synthesis of the key intermediate **18** starting from benzoic acid is shown in Scheme 6 (overall yield 25%). Alkylation of the methyl ester of 2,5-cyclohexadiene carboxylic acid (90% from benzoic acid)[13] with chloromethyl benzyl ether and lithium diisopropylamide as the base gave 75% yield of substituted ester which was reduced with LAH to the alcohol **21** (94%). The base induced double bond migration afforded (93% yield) a 9:1 mixture of **22** and **21**. Transformation into the corresponding diazomalonic ester **23** involved treat-



Scheme 4.

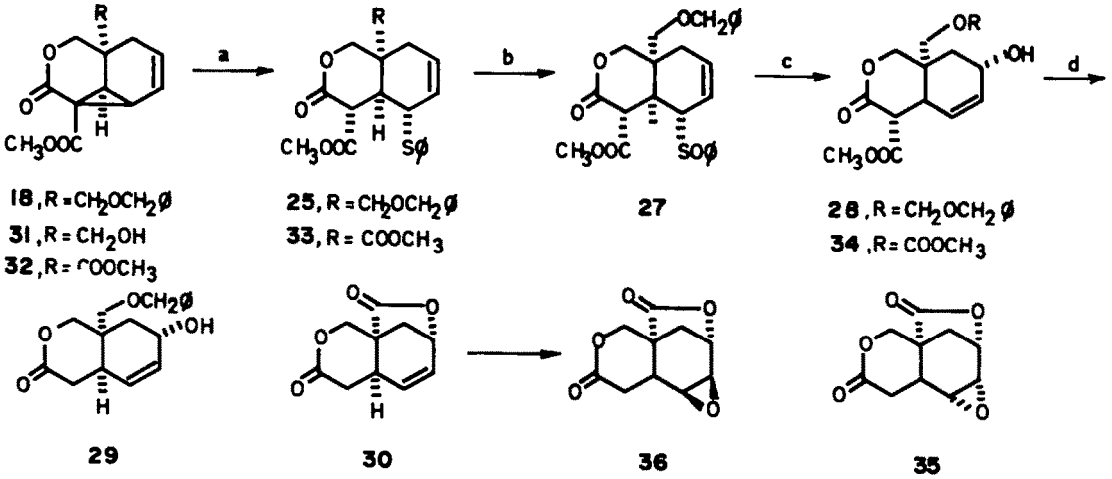


Scheme 6. a, LDA, −78°C, THF-HMPA, $ClCH_2OCH_2\phi$; b, LAH, ether; c, t.BuOK, DMSO, r.t.; d, $ClCOCH_2COOMe$, C_5H_5N, ether; e, TsN_3, Et_3N, CH_3CN; f, $Cu(acac)_2$, toluene, reflux.

ment with methyl malonyl chloride (95%) and subsequent reaction with tosylazide and triethylamine (92%). The carbenoid cyclopropanation reaction(62%) was finally performed in refluxing toluene with cupric acetyl acetonate as catalyst.

By analogy with the conversion of **6** to **20**, the acetate **24** was expected from **18** under solvolytic conditions (acetic acid–sulfuric acid). Unfortunately, all attempts to effect solvolytic ring cleavage of the olefin **18** led to complex mixtures in which the presence of **24** could not be detected. This failure prevents the use of intermediates of type I' (*vide supra*). The cyclopropane ring opening with sodium thiophenolate and subsequent transformation to the isomeric allylic alcohol of type **i** (*vide supra*) proved more rewarding (Scheme 7). Treatment of **18** with sodium thiophenolate in refluxing methanol led to a mixture of the expected **25** and decarboxylated product **26**, in contrast with previous results (**6**→**19**). Although **29** is the desired target in this sequence, the reaction conditions for simultaneous decarboxylation to form **26** could not be optimalized. Milder conditions (dimethyl sulfoxide at room temp) afforded pure **25** (m.p. 97°) in good yield (86%).

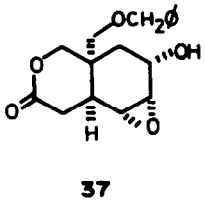
The large coupling constant value found for H-4 ($^3J_{4,5}$ = 10.8 Hz) corroborates the stereochemistry at C-4. The diastereoisomeric sulfoxides **27** obtained upon oxidation with *m*-chloroperbenzoic acid were directly rearranged with trimethyl phosphite in refluxing methanol to the allylic alcohol **28** (81% yield from **25**). Saponification and subsequent acid treatment finally afforded the allylic alcohol **29** (70% isolated yield). With the synthesis of the alcohol **29** we have attained a primary goal in our design (formation of **i**); at this point we felt that a more definite proof for the proposed structure was needed. We therefore examined the transformation of **29** into the bis-lactone **30**, the formation of which would provide us with an absolute structural assignment. Because of the obvious danger of transesterification to the *trans*-fused 2-oxa-3-decalone system upon cleavage of the benzyl ether in **29**, we decided to transform the angular function at an earlier stage where this damaging process could not take place. Treatment of the tricyclic olefin **18** with boron tribromide in methylene chloride at −78° afforded the alcohol **31** in low yield (32%) when large scale reactions (1.5×10^{-2} mole) were carried out although small scale (6.0×10^{-4} mole) experiments have given yields up to 70%. Other current methods for ether cleavage such as hydrogenolysis, trimethylsilyl iodide and acetic anhydride-ferric chloride or boron trifluoride, led to disappointing results. Jones oxidation and subsequent esterification with diazomethane afforded **32** (m.p. 118–120°) in 66% isolated yield. This product was taken through the reaction sequence depicted in Scheme 7 (as for **18**→**28**) and led, via **33**, to the allylic alcohol **34** in 59% overall yield. The bis-lactone **30** (ν, 1764 and 1734 cm^{-1}) was finally obtained upon saponification and subsequent treatment with acetic acid–acetic anhydride (80°, 2 hr) in 60% yield. Although at this point **30** had served its purpose, it was nevertheless worthwhile to examine its transformation to the epoxide **35**, which in the course of our work had been synthesized and transformed into vernolepin by Danishefsky *et al.*[4b] Not surprisingly, epoxidation of **30** with *m*-chloroperbenzoic



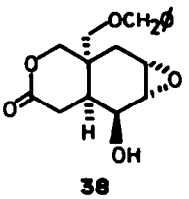
Scheme 7. a, $NaS\phi$, DMSO, r.t.; b, m.CPBA, CH_2Cl_2, −78°C; c, $(MeO)_3P$, MeOH, reflux; d, K_2CO_3, MeOH-H_2O, reflux; H_2SO_4; benzene, reflux.

acid (6 days) led only to **36** in 78% yield. The physical and spectroscopic data obtained for **36** (m.p. 144–147°) were clearly different from those reported[4b] for the isomeric epoxide **35** (m.p. 172–173°). The olefin **30** did not react with Payne's reagent[15] even after prolonged reaction times (7 days); there is an example[16] of preferential attack of this reagent from a concave side of a molecule.

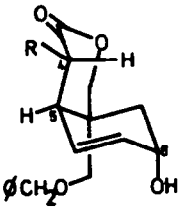
On the other hand, epoxidation of the allylic alcohol **29** with *m*-chloroperbenzoic acid in methylene chloride (4 days) led to two epoxides in 62% yield (ratio 1:1), to



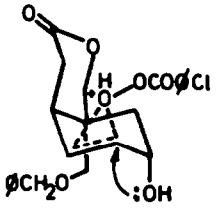
37



38



29a, R = H
28a, R = $COOCH_3$

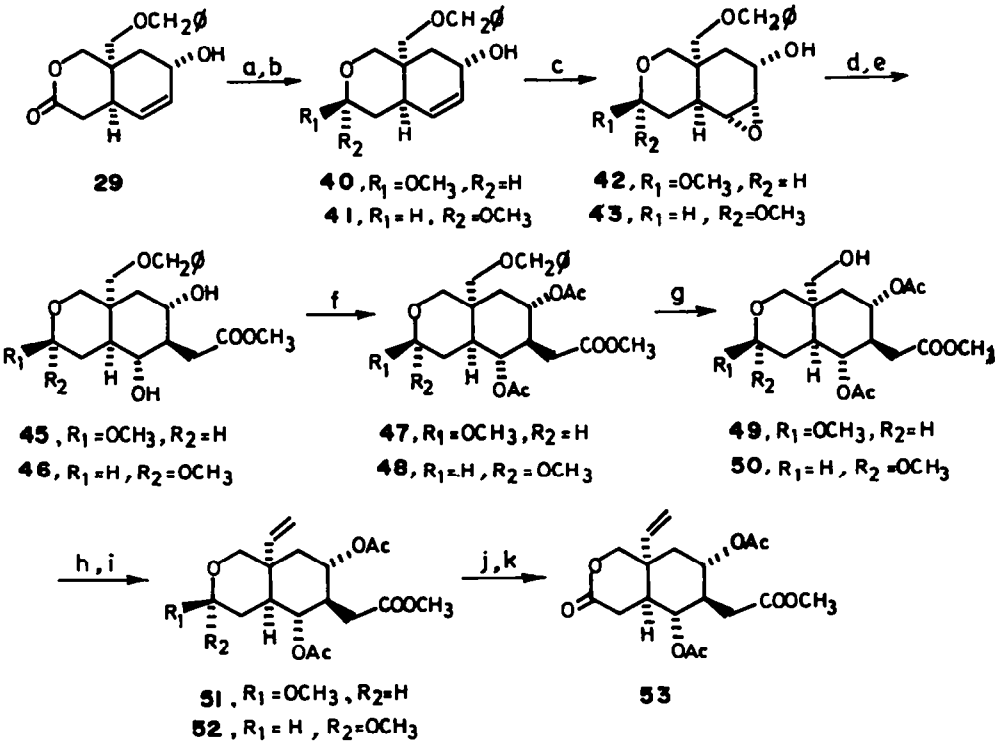


39

Scheme 8.

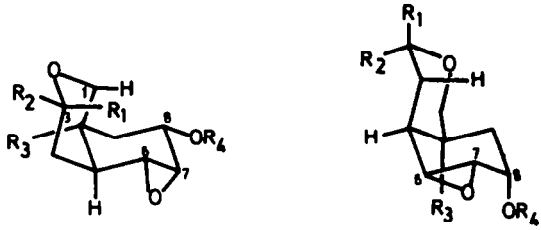
which structures **37** and **38** were assigned. With regard to the known stereo-directing influence[17] of an allylic hydroxyl group in peracid oxidation this result came as a surprise. Structure **37** was assigned to the expected "Henbest-type" epoxide, since the same product (tlc and ^1H NMR analysis) was formed as the sole epoxide (39% isolated yield), next to starting material and an enone (UV light absorbance on tlc monitoring), upon oxidation with t-butyl hydroperoxide and a catalytic amount of vanadyl acetylacetonate in benzene where the syn-directive effect of an alcohol is known to be very pronounced.[18] The ^1H NMR spectral data of **37**, especially the vicinal coupling constant values obtained for H-8 (dd, ^3J = 11.0 and 5.5 Hz), are in accordance with the conformation where the angular benzyloxy Me group is equatorially located on the cyclohexane ring. The other epoxide was identified as **38** on ^1H NMR spectral ground (Experimental) and would arise from β-attack of the peracid and facile intramolecular displacement by the axial 8-OH function (**39**). This result and the similarity between the ^1H NMR spectra of **28** and **29** (e.g. $\Sigma^3J_{H\text{-}8}$ = 14.5 Hz for **28** and 14.4 Hz for **29**) led us to assume that the conformational equilibrium of the starting allylic alcohol is in favor of **29a**; indeed, the large value found in **28** for the coupling constant between H-4 and H-5 (9.6 Hz) indicates **28a** as the preferred conformation.

This led us to perform first the necessary δ-lactone protection thereby hoping that the change in hybridization of C-3 would generate another conformational behaviour of the allylic alcohols **40** and **41**. Reduction of **29** with diisobutylaluminum hydride in toluene (−60°), followed by treatment with methanol and a trace of sulphuric acid (2 hr) yielded the diastereoisomeric acetals **40** and **41** (80% yield) which could not be separated at this stage. Subsequent fast epoxidation with *m*-chloroperbenzoic acid in methylene chloride (3 hr!) led to two



Scheme 9. a, DiBAH, C_7H_8, −60°C; b, MeOH, H_2SO_4, 2 hr; c, m.CPBA, CH_2Cl_2, 3 h; d, $LiCH_2COOLi$, DME; e, CH_2N_2; f, Ac_2O, C_5H_5N; g, 10% Pd on C, H_2, EtOH; h, $CrO_3(C_5H_5N)_2$, CH_2Cl_2; i, $CH_2 = P\phi_3$, DME; J, CH_3CN, HCl, H_2O; k, Ag_2CO_3/celite, C_6H_6, reflux.

epoxides easily separable on silica gel using ethyl acetate-isooctane (7:3) as eluent. The less polar isomer (45% isolated yield) was identified as **42** and the more polar isomer (39% isolated yield) as **43** on the following grounds (Scheme 10): (a) the α-orientation was assigned to the epoxide ring in both products, since the same two epoxides were formed, next to enone **44**, upon epoxidation with t-butyl hydroperoxide, catalyzed by vanadyl acetyl acetonate;[18] (b) the stereodishomogenity was attributed to the chiral center at C-3 where the sum of the vicinal coupling constants of H-3 clearly allows differentiation between **42** (β-OMe; $\Sigma^3J = 6.0$ Hz) and **43** (α-OCH_3; $\Sigma^3J = 12.0$ Hz). The remaining ^1H NMR spectral data are in accordance with the proposed conformations **42e** and **43e** (large trans $^3J_{8,9}$; respectively



e

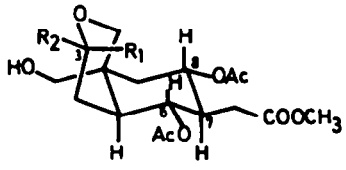
a

42, $R_1 = OCH_3$, $R_2 = H$, $R_3 = CH_2OBz$, $R_4 = H$

43, $R_1 = H$, $R_2 = OCH_3$, $R_3 = CH_2OBz$, $R_4 = H$

54, $R_1, R_2 = -OCH_2CH_2O-$, $R_3 = CH{=}CH_2$, $R_4 = H$

55, $R_1 = OCH_3$, $R_2 = H$, $R_3 = CH{=}CH_2$, $R_4 = CH_2OCH_3$

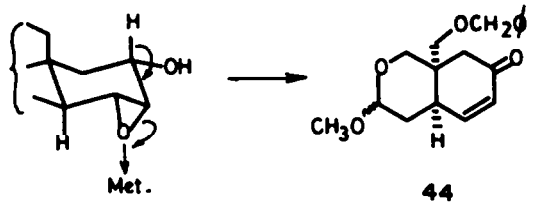


49, $R_1 = OCH_3$, $R_2 = H$

50, $R_1 = H$, $R_2 = OCH_3$

Scheme 10. ^1H NMR ($CDCl_3$) **49**: $^3J_{H\text{-}8} = 10.8, 10.8, 4.8$ Hz; $^3J_{H\text{-}6} = 10.2, 10.2$ Hz; $\Sigma^3J_{H\text{-}3} = 6.5\text{-}7$ Hz: **50**: $^3J_{H\text{-}8} = 11.1, 11.1, 4.8$ Hz, $^3J_{H\text{-}6} = 10.5, 10.5$ Hz, $\Sigma^3J_{H\text{-}3} = 11.7$ Hz.

10.8 Hz and 9.6 Hz). This result suggests a different conformational behaviour for **40** and **41**, in comparison with **29** (Scheme 8); unfortunately, this phenomenon could not be checked by ^1H NMR analysis due to the occurrence of an unseparable epimeric mixture. The enone **44** is supposedly formed by intramolecular transition metal-activated epoxide ring opening, followed by elimination of the OH group at C-6. Here the enone is the major reaction product from the transition metal catalyzed epoxidation and is even exclusively formed upon prolonged reaction times;[a] similar results have been reported in the literature.[19]



Scheme 11.

Although the final sequence (Scheme 9) can in principle be performed on the mixture of **42** and **43**, the preference was given to performing the opening of the hydroxy-epoxides with dilithioacetate[20] on the pure isomers for two reasons: (a) structural analysis (especially ^1H NMR) would be greatly simplified, (b) the behaviour of both epoxides towards ring opening could, based on the results of Danishefsky[4b] and Schlessinger[11b] be damagingly different. Indeed, Danishefsky *et al.* found that, although conformer **54e** in which the substituents on the B ring are equatorial would predominate at equilibrium, axial attack of the incoming nucleophile (in casu dilithioacetate) occurred at C-7 in the higher energy conformer **54a**; this result was attributed on the ground that the path for diaxial opening in the more stable conformer **54e** is highly encumbered by the axial oxygen (R_1: Scheme 10) of the ethylene orthoester. The same result was observed by Schlessinger for the similar nucleophilic epoxide opening (using t-butyl dilithioacetoacetate[11a]) of **55**: only attack at C-7 occurred (R_1 = OMe in **55**). We did expect an identical result for the α-hydroxy epoxide **42**; on the other hand, such steric hindrance is not present in **43** (R_1 = H) so that here nucleophilic attack at C-6 could occur in the low energy chain conformer **43e**. As a matter of fact reaction of dilithioacetate on both epoxides occurred at C-7 yielding the desired diols **45** and **46** after esterification with diazomethane (70%). This result strongly suggests that the nonreactivity of the low-energy conformer **e** is due to yet another reason than the one invoked by Danishefsky. The axial location of two substituents (R_1 and H) on the A-ring could indeed prevent reaction of these **e**-conformers whatever the nature of R_1 (alkoxy as in **42**, **54** and **55** or hydrogen as in **43**); previous results reported in the literature are in accord with this rationalization.[21] The protective benzyl ether group was removed on the corresponding diacetates (**47** and **48**; 81.3%) by hydrogenolytic cleavage (93%). Confirmation of the proposed structures, especially regarding the trans relation of the three substituents on the B ring is found in the ^1H NMR where the large vicinal coupling constant values found for H-6 and H-8 are very indicative.

Final transformation into Grieco's lactone **53**, involved oxidation of the alcohol function, followed by reaction with methylene triphenylphosphorane to **51** and **52** (47%), deprotection of the acetal in acid and oxidation of the lactol **53** with silver carbonate on celite[22] (48%). Physical and spectroscopic data were in accordance with literature data.[2b,b] Since **53** has been converted into (±)-vernolepin and (±)-vernomenin our synthesis of this lactone constitutes a novel total synthesis of the racemic natural products.

[a] Under these conditions 2-cyclohexenol was found to yield 2-cyclohexenone via the corresponding epoxide (tlc).

[b] We are indebted to Prof. Grieco for having recorded the ^1H NMR spectrum of a sample of **53** and for comparison with his results.

EXPERIMENTAL

The m.ps are uncorrected. The IR spectra were recorded on a Perkin–Elmer 337 spectrophotometer and the NMR spectra at 90

MHz (Varian EM-390 spectrometer) in $CDCl_3$ unless otherwise stated with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. The mass spectra and exact mass measurements (HR) were recorded on an AEI MS-50 spectrometer. R_f values are quoted for Merck silica gel 60 GF_{254} tlc plates of thickness 0.25 mm with ethyl acetate–isooctane (ratio given between brackets) as eluent unless otherwise stated. Reaction products were isolated by the addition of water and extracted with the specified solvent. The combined extracts were washed with saturated brine and dried over $MgSO_4$. The solvent was removed from the filtered solns on a rotary evaporator. Column chromatographic separations were performed on silica gel with ethyl acetate-isooctane (ratio given between brackets) as eluent unless otherwise stated.

1 - *Benzyloxymethyl* - 1 - *hydroxymethyl* - 2, 5 - *cyclohexadiene* (21). A soln of 1,4-dihydrobenzoic acid[13] (60 g; 0.5 mol) in MeOH (75 ml), benzene (225 ml) and H_2SO_4 (3 ml) was refluxed for 5 hr. The mixture was poured in Na_2CO_3 soln (8%, 100 ml) and ether (100 ml) and the crude methyl 1,4-dihydrobenzoate isolated in the usual way and purified by distillation (62 g; 90%): b.p. 80° at 20 mm Hg. The ester (6.9 g; 0.05 mol) in THF (70 ml) was added dropwise at −78° to a soln of LDA (0.06 mol) in THF (55 ml). After the addition of HMPA (7 ml), a soln of chloromethylbenzyl ether (8 g; 0.051 mol) in THF (30 ml) was added dropwise at −78°. Stirring was continued for 1 hr and the temp raised to −20°. The mixture was poured into sat NaCl soln (100 ml). The product was isolated with ether and purified by distillation, yielding 1-benzyloxymethyl-1-methoxycarbonyl-2,5-cyclohexadiene (9.6 g; 75%): b.p. 125° at 0.001 mm Hg; R_f (ether-isooctane, 1:1) 0.41; IR (film) 1748, 1508 cm^{-1}; NMR 7.26(s,5), 5.83(s,4), 4.48(s,2), 3.68(s,3), 3.52(s,2), 2.66(s,2); MS m/z 258 (M^+, 3), 138(64), 107(68), 91(95), 92(100), 93(91). To a suspension of LAH (14.7 g; 0.369 mol) in ether (500 ml) was added dropwise a solution of 1 - benzyloxymethyl - 1 - methoxycarbonyl - 2, 5 - cyclohexadiene (95.1 g; 0.369 mol) in ether (500 ml). The mixture was cautiously quenched with EtOAc and acidified with dil HCl aq (20%). Water was added and the product isolated with ether. Distillation of the residue yielded 21 (79.9 g; 94%): b.p. 120° at 0.001 mm Hg; R_f (ether–isooctane, 1:1) 0.22, IR (film) 3600–3100 cm^{-1}; NMR 7.35 (s,5), 5.90 (dt, J = 10.5, −3.3 and 3.3 Hz), 5.64 (dt, J = 10.5, 1.8 and 1.8 Hz, 2), 4.54 (s,2), 3.59 (s,2), 3.43 (s,2), 2.70 (m,2); MS m/z 230 (M^+, 0.05), 92 (42), 91 (100).

The conjugated diene 22. To a soln of 21 (40 g; 0.174 mol) in DMSO (500 ml) was added in a few min a soln of t-BuOK (39 g; 0.348 mol) in DMSO. After stirring for 3.5 hr, water (1 l) was added dropwise at 0° followed by HCl (pH 5). The product was isolated with ether and distilled, yielding 37 g (93%) of a 9:1 mixture of 22 and 21. An analytically pure sample was obtained by column chromatography (ether–isooctane, 1:1) b.p. 120° at 0.001 mm Hg; R_f (ether-i.oct, 1:1) 0.26; IR (film) 3600–3100 cm^{-1}; NMR 7.38 (s,5), 6.2–5.5 (m,4), 4.55 (s,2), 3.59 (s,2), 3.44 (s,2), 2.26 (d, J = 3 Hz, 2); MS m/z 230 (M^+,4), 182 (7) 122 (34), 121 (40), 92 (92), 91 (100).

The diazomalonic ester 23. To a soln of 22 (37 g, 0.160 mol) and pyridine (19.5 ml; 0.241 mol) in ether (400 ml) was added dropwise at 0° a soln of methyl malonyl chloride (28.5 g; 0.209 mol) in ether (400 ml). After 30 min, sufficient ice-water was added to bring the ppt into soln and stirring was continued for 1 hr at r.t. After washing with dil HCl and sat Na_2CO_3, ether was evaporated and the residue was purified by column chromatography (1:9), yielding 45 g (85%) of the methyl malonic ester. R_f (ether–isooctane, 1:1) 0.37; IR (film) 1750 cm^{-1}; NMR 7.35 (s,5), 6.2–5.5 (m,4), 4.53 (s,2), 4.18 (s,2), 3.75 (s,3), 3.37 (s,2; s,2), 2.20 (m,2); MS m/z 212 (0.5), 209 (1), 121 (1), 105 (4), 101 (6), 92 (25), 91 (100).

To a soln of the ester (45.0 g; 0.136 mol) and Et_3N (19 ml; 0.136 mol) in dry acetonitrite (200 ml) was added a soln of *p*-toluenesulfonyl azide (30.9 g, 0.157 mol) in dry acetonitrile (200 ml). The mixture was stirred overnight, concentrated *in vacuo* and the residue taken up in ether. The soln was washed with water (240 ml) containing KOH (9.6 g), with 120 ml of water (120 ml) containing KOH (4.8 g) and with water 120 ml). Workup and column chromatography (1:9) yielded 23 (44.7 g; 92%). R_f (ether–isooctane, 1:1) 0.35; IR (film) 2125, 1758, 1733, 1689, 1445 cm^{-1}; NMR 7.37 (s,5), 6.2–5.5 (m,4), 4.53 (s,2), 4.27 (s,2), 3.85 (s,3), 3.42 (s,2), 2.27 (m,2); MS m/z 265 (0.1), 235 (5), 104 (15), 92 (39), 91 (100).

The cyclopropanation of 23. A soln of 23 (4.5 g; 12.6 mmol) and copper(II) acetylacetonate (450 mg) in toluene (400 ml) was heated at reflux for 30 min under vigorous stirring, cooled to room temp. and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and washed with dil H_2SO_4 (10%) and water. Workup and column chromatography (2:3) yielded 18 (2.55 g; 62%): R_f (1:1) 0.31; IR (film) 1750 cm^{-1}; NMR 7.37 (s,5), 5.93 (ddd, J = 10.2, 4.8 and 2.4 Hz, 1), 5.76 (dt, J = 10.2, 3.3 and 3.3 Hz), 4.53 (s,2), 4.36 (d, J = 10.8 Hz, 1), 3.94 (d, J = 10.8 Hz, 1), 3.76 (s,3), 3.40 (s,2), 2.54 (dd, J = 9.0 and 3.3 Hz), 2.26 (d, J = 9.0 Hz, 1), 2.3–2.1 (m,2); MS m/z 328 (M^+,4), 329 (2.5), 297 (4), 296 (3), 237 (12), 92 (41), 91 (100); HR: M^+. Found: 328.1379. $C_{19}H_{20}O_5$ requires: 328, 1311.

Formation of sulfide 25. To a soln of 18 (16.36 g; 0.05 mol) in DMSO (160 ml) was added dropwise under N_2 a soln of dry sodium thiophenolate (55.6 mmol) in DMSO (100 ml). After 15 min the mixture was poured in water (700 ml) and acidified with dil H_2SO_4. Isolation with ether and purification by column chromatography (1:9 for ϕSH and 3:7 for 25) yielded 25 (18.8 g; 86%): R_f (benzene–EtOAc, 9:1) 0.41; m.p. 97°. (Found: C, 67.6, H, 5.89, $C_{25}H_{26}O_5S$ requires C, 68.5%, H, 5.98%); IR (film) 1760 cm^{-1}; NMR 7.30 (m,10), 5.83 (m,2), 4.59 (d, J = 12.0 Hz, 1), 4.48 (d, J = 12.0 Hz, 1), 4.40 (d, J = 12.0 Hz, 1), 4.16 (d, J = 12.0 Hz, 1), 3.62 (s,2), 3.49 (m,1), 3.45 (s,3), 3.30 (d, J = 10.8 Hz, 1), 2.78 (dd, J = 10.8 and 1.8 Hz, 1), 2.13 (m,2); MS m/z 438 (M^+, 0.8), 406 (14), 92 (28), 91 (100).

The allylic alcohol 28. To a soln of 25 (7.4 g; 16.9 mmol) in CH_2Cl_2 (200 ml) was added dropwise at −78° a soln of m-chloroperbenzoic acid (3.77 g; 18.6 mmol) in CH_2Cl_2 (100 ml). After 15 min the mixture was poured in CH_2Cl_2 (300 ml) and was washed with 4% Na_2SO_3 aq (80 ml) and with sat Na_2CO_3 aq. Workup yielded 27 sufficiently pure for further use.

A soln of the crude 27 and trimethyl phosphite (5.5 ml; 46.7 mmol) in abs MeOH (100 ml) was heated at reflux for 2 hr; trimethyl phosphite (1.5 ml) was added and the reaction was continued for 90 min. The mixture was cooled, concentrated *in vacuo*, treated with dry toluene (100 ml), concentrated *in vacuo*. The residue was purified by column chromatography (7:3), yielding 28 (4.73 g; 81%): R_f (EtOAc) 0.48; IR (film) 3700–3100, 1754, 1740 cm^{-1}; NMR 7.30 (s,5), 5.99 (ddd, J = 9.9, 3.6 and 1.8 Hz), 5.63 (ddd, J = 9.9, 3.6 and 1.2 Hz), 4.54 (s,2), 4.25 (d, J = 11.7 Hz, 1), 4.21 (m,1), 3.92 (d, J = 11.7 Hz, 1), 3.81 (s,3), 3.46 (s,2), 3.26 (d, J = 9.6 Hz, 1), 2.77 (m,1), 1.88 (dd, J = 14.3 and 5.1 Hz), 1.74 (dd, J = 14.3 and 5.8 Hz); MS m/z 220 (7), 219 (12), 218 (100).

The allylic alcohol 29. A soln of 28 (11.35 g; 32.8 mmol) and K_2CO_3 (18.4 g; 0.133 mol) in MeOH (110 ml) and water (45 ml) was vigorously stirred at reflux temp. for 2 hr. The mixture was cooled and the MeOH evaporated *in vacuo*. The water phase was acidified with a soln of H_2SO_4 (14 ml) in water (100 ml) and extracted with $CHCl_3$ and EtOAc. The residue obtained after workup was taken in dry benzene (200 ml) and heated at reflux for 75 min. The mixture was cooled, concentrated *in vacuo* and the product isolated with ether. Workup and column chromatography (3:2) yielded 29 (6.58 g; 70%): R_f (EtOAc) 0.44; IR (film) 3600–3100, 1732 cm^{-1}; NMR 7.30 (s,5), 5.93 (ddd, J = 10.2, 3.0 and 1.5 Hz), 5.59 (ddd, J = 10.2, 3.0 and 1.2 Hz), 4.53 (s,2), 4.24 (m,1), 4.22 (d, J = 12.0 Hz, 1), 3.95 (d, J = 12.0 Hz, 1), 3.41 (s,2), 3.0–2.0 (m,3), 1.89 (dd, J = 13.8 and 4.6 Hz), 1.66 (dd, J = 13.8 and 6.8 Hz); MS m/z 288 (M^+, 0.15), 197 (1), 149 (10), 91 (100), 92 (32).

The alcohol 31. To a soln of 18 (1.53 g; 4.67 mmol) in CH_2Cl_2 (30 ml) was added at −78° freshly destilled BBr_3 (1.8 ml; 19 mmol). After stirring for 15 min the temp was raised to −40° and the mixture rapidly quenched with a Na_2CO_3 (7 g) aq. The mixture was brought to room temp and the water phase extracted (6×) with $CHCl_3$. After workup and column chromatography (4:1) 31 (0.73 g; 66%) was obtained: R_f (EtOAc) 0.37; IR (film) 3600–3100, 1750 cm^{-1}; NMR 5.97 (ddd, J = 9.9, 5.1 and 2.4 Hz, 1), 5.76 (m,1), 4.39 (d, J = 10.8 Hz, 1), 3.96 (d, J = 10.8 Hz, 1), 3.77 (s,3), 3.65 (s,2), 2.57 (dd, J = 9.0 and 3.65 Hz, 1), 2.33 (d, J = 9.0 Hz, 1); MS m/z 239 (4), 238 (M^+, 11), 207 (38), 206 (80), 91 (100).

The methyl ester 32. To a soln of 31 (430 mg; 1.81 mmol) in

acetone (9 ml) was added dropwise at 0° Jones reagent (1.8 ml; 2.06 N). Excess reagent was destroyed after 30 min by the dropwise addition of i-PrOH. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in acetone (5 ml) and treated with CH_2N_2. Workup and purification by column chromatography (1:1) yielded **32** (317 mg; 66%): m.p. 118–120°; R_f (1:1) 0.24; IR (KBr) 1740, 1638, 1617 cm^{-1}; NMR 5.95 (ddd, J = 9.9, 5.1 and 1.8 Hz, 1), 5.83 (m,1), 4.46 (d, J = 11.1 Hz, 1), 4.19 (d, J = 11.1 Hz, 1), 3.79 (s,3), 3.77 (s,3), 2.94 (d, J = 8.4 Hz, 1), 2.9–2.1 (m,3); MS m/z 266 (1), 236 (2), 235 (8), 234 (20), 204 (28), 203 (100).

The allylic alcohol **34**. In the same manner as **28** was obtained from **18**, the ester **32** yielded, via the sulfide **33** (80% yield; purified by column chromatography, benzene–EtOAc, 85:15; m.p. 112–114°; R_f (1:1) 0.34), the alcohol **34** (74% yield; purified by column chromatography, 9:1): R_f (EtOAc) 0.37; IR (film) 3700–3100, 1760, 1740 cm^{-1}; NMR 5.97 (ddd, J = 10.2, 3.3 and 1.8 Hz, 1), 5.66 (ddd, J = 10.2, 3.6 and 1.2 Hz, 1), 4.59 (d, J = 12.0 Hz, 1), 4.26 (m,1), 4.14 (d, J = 12.0 Hz, 1), 3.82 (s,3), 3.76 (s,3), 3.72 (m,1), 3.29 (d, J = 9.0 Hz, 1), 2.03 (m,2); MS m/z 253 (0.6), 44 (100).

The bis-lactone **30**. The alcohol **34** (240 mg; 0.845 mmol) and K_2CO_3 (352 mg; 2.55 mmol) were heated at reflux in MeOH (5 ml) for 2 hr. The mixture was cooled and concentrated *in vacuo*. To the residue were added AcOH (0.292 ml; 5.1 mmol) and Ac_2O (8 ml). The mixture was slowly heated to 80° and stirred for 2 hr. After cooling and concentrating *in vacuo* (1 mm Hg), the residue was taken up in water and acidified with dil H_2SO_4. Isolation with $CHCl_3$ and column chromatography (benzene–EtOAc, 1:1) yielded **30** (82 mg; 50%): R_f (EtOAc) 0.44; IR (KBr) 1764, 1730 cm^{-1}; NMR 6.34 (ddd, J = 9.6, 5.4 and 1.5 Hz, 1), 5.81 (dd, J = 9.6 and 3.3 Hz, 1), 4.89 (m,1), 4.71 (d, J = 12.0 Hz, 1), 4.30 (d, J = 12.0 Hz, 1), 3.2–2.0 (m,5), MS m/z 195 (1), 194 (M^+,1), 178 (1), 150 (3), 92 (25), 91 (41), 44 (100).

The epoxide **36**. A sol of **30** (31 mg; 0.16 mmol) and 85% m-CPBA (130 mg) in CH_2Cl_2 (0.6 ml) was stirred for 6 days at room temp. After addition of CH_2Cl_2 (3 ml) the excess reagent was extracted with a soln of Na_2SO_3 (150 mg; 1.2 mmol) in water (1 ml). The organic phase was washed with a sat Na_2CO_3 aq. Workup yielded **36** (26 mg; 78%): m.p. 143–147°; R_f (benzene–EtOAc, 1:1) 0.30; IR (KBr) 1778, 1746 cm^{-1}; NMR (pyridine) 5.11 (dd, J = 3.6 and 5.4 Hz, 1), 4.71 (d, J = 12.0 Hz, 1), 4.20 (d, J = 12.0 Hz, 1), 3.57 (t, J = 3.6 Hz, 1), 3.21 (t, J = 3.6 Hz, 1), 2.99 (m,2), 2.73 (m,1), 2.49 (d, J = 12.6 Hz, 1), 1.97 (dd, J = 12.6 and 5.4 Hz, 1); MS m/z 165 (1), 156 (3), 91 (24), 39 (100).

Epoxidation of **29**. A soln of **29** (123 mg; 0.427 mmol) and 85% *m*-CPBA (104 mg; 0.512 mmol) in CH_2Cl_2 (2 ml) was stirred for 4 days at room temp; after addition of more oxidant (217 mg) the reaction was continued for 2 days. Workup, as described for **36** and column chromatographic (85:15) separation yielded **37** (40 mg, 31%) and **38** (40 mg, 31%). For **37**: R_f (EtOAc) 0.31; IR (film) 3600–3100, 1748 cm^{-1}; NMR (300 MHz, $CDCl_3$) 7.4–7.2 (m,5), 4.50 (d, J = 12.0 Hz, 1), 4.48 (d, J = 12.0 Hz, 1), 4.29 (d, J = 11.8 Hz, 1), 4.19 (dd, J = 11.0 and 5.5 Hz, 1), 3.96 (d, J = 11.8 Hz, 1), 3.35 (d, J = 4.25, 1), 3.28 (d, J = 9.0 Hz, 1), 3.15 (d, J = 9.0 Hz, 1), 3.07 (dd, J = 4.25 and 0.5 Hz), 2.81 (dd, J = 17.0 and 8.5 Hz, 1), 2.38 (m,2), 1.69 (dd, J = 11.0 and 13.5 Hz, 1) and 1.61 (dd, J = 13.5 and 5.5 Hz, 1); MS m/z 175 (2), 174 (17), 148 (100). For **38**: R_f (EtOAc) 0.41; IR (film) 3600–3100, 1739 cm^{-1}; NMR (300 MHz, $CDCl_3$) 7.4–7.2 (m,5), 4.60 (d, J = 11.8 Hz, 1), 4.57 (d, J = 11.8 Hz, 1), 4.24 (m,1), 3.87 (d, J = 12.0 Hz, 1), 3.75 (d, J = 12.0 Hz, 1), 3.48 (d, J = 8.8 Hz, 1), 3.31 (m,1), 3.30 (d, J = 8.8 Hz, 1), 3.18 (t, J = 3.5 Hz, 1), 2.65 (m,2), 2.36 (ddd, J = 11.0, 6.25 and 3.0 Hz, 1), 1, 73 (dd, J = 15.0 and 3.5 Hz, 1), 1.51 (d, J = 15.0 Hz, 1).

The epoxides **42** *and* **43**. DIBAH (6.59 mmol) in toluene (3.74 ml of a 25% soln) was added dropwise at −60° to **29** (863 mg; 3.0 mmol) in toluene (20 ml); after stirring for 15 min the soln was added via a syringe to 15 ml water. Acidification with dil H_2SO_4 and isolation with ether gave 870 mg crude product which was dissolved in abs MeOH (10 ml) containing 1 drop H_2SO_4. After stirring at r.t. for 90 min, pyridine (0.2 ml) was added and the solvent was removed *in vacuo*. Isolation with ether and column chromatography (35:65) yielded a mixture of **40** and **41** (726 mg; 80%): R_f (EtOAc) 0.54. *m*-CPBA (574 mg; 2.84 mmol) was added to the mixture of **40** and **41** (576 mg; 190 mmol) in CH_2Cl_2 (12 ml). The mixture was stirred for 3 hr at room temp and worked up as described for **36**. Separation by column chromatography (7:3) yielded epoxides **42** (275 mg; 45%) and **43** (238 mg, 39%). For **42**: m.p. 89–90°(Found: C, 67.3, H, 7.41. $C_{18}H_{24}O_5$ requires: C, 67.5, H, 7.55%); R_f (4:1) 0.33; IR (KBr) 3600–3200 cm^{-1}; NMR 7.35 (s,5), 4.56 (m,1), 4.54 (d, J = 12.6 Hz, 1), 4.46 (d, J = 12.6 Hz, 1), 4.05 (ddd, J = 10.8, 6.6 and 1.8 Hz), 3.8–3.1 (m,6), 3.29 (s,3), 2.1–1.2 (m,5); MS m/z 271 (0.4), 179 (6.5), 105 (19), 91 (100). For **43**: m.p. 97–99°; R_f (4:1) 0.25; IR (KBr) 3600–3200 cm^{-1}; NMR 7.32 (s,5), 4.47 (s,2), 4.46 (m,1), 4.18 (ddd, J = 9.6, 6.3 and 2.4 Hz), 3.8–3.1 (m,4), 3.39 (s,3), 3.32 (s,2), 2.3–1.3 (m,5); MS m/z 271 (0.3), 121 (7), 105 (11), 91 (100).

Transition metal catalyzed hydroperoxide epoxidation of **40** *and* **41**. A soln of **40** and **41** (35 mg; 0.115 mmol) and of vanadyl (IV) acetylacetonate (2 mg; 7.6×10^{-3} mol) in benzene (0.75 ml) was heated at reflux for 2 min. After the dropwise addition of t-butylhydroperoxide (17 μl; techn.) and a further 8 μl after 1 hr, stirring was continued at reflux temp for 2 hr. The mixture was cooled and concentrated *in vacuo*. Purification of the residue by column chromatography (1:1) yielded 16 mg (46%) of enone **44** as a diasteroisomeric mixture: R_f (EtOAc) 0.54; IR (film) 1678 cm^{-1}; NMR 7.30 (s,5), 6.9–6.7 (dd, J = 9.9 and 3.9 Hz; dd, J = 9.9 and 2.7 Hz, 1), 6.0–5.9 (d, J = 9.9 Hz, 1), 4.7–4.5 (m,1), 4.48 and 4.42 (2s,2), 3.9–3.3 (m,4), 3.37 and 3.33 (2s,3), 3.0–1.2 (m,5).

The diols **45** *and* **46**. To a soln of LDA (0.19 mol) in DME (155 ml), AcOH (5.32 ml, 93 mmol) in DME (20 ml) was added dropwise at −40°. After stirring for 90 min at 40°, epoxide **42** (1.73 g; 5.47 mmol) in DME (15 ml) was added to the white suspension. The mixture was heated for 40 hr at 60°, cooled to −10°, quenched with water (20 ml) and acidified with dil H_2SO_4. Extraction with EtOAc yielded an oil, which was taken in toluene; the residue obtained after evaporation *in vacuo* was dissolved in acetone and treated with CH_2N_2. Workup and column chromatography (3:1) yielded **45** (1.48 g; 70%): R_f (EtOAc) 0.37; IR (film) 3600–3100, 1730 cm^{-1}; NMR 7.33 (s,5), 4.59 (d, J = 3.0 Hz, 1), 4.54 (d, J = 12.6 Hz, 1), 4.47 (d, J = 12.6 Hz, 1), 3.64 (s,3), 4.0–3.1 (m,6), 3.27 (s,3), 2.65 (d, J = 5.4 Hz, 2), 2.2–1.4 (m,6); MS m/z 363 (0.02), 241 (2), 91 (100). The same procedure was followed for the conversion of epoxide **43** into diol **46**: R_f (EtOAc) 0.36; NMR 7.30 (s,5), 4.51 (s,2), 4.42 (m,1), 3.67 (s,3), 3.43 (s,3), 4.0-3.0 (m,6), 2.69 (m,2), 2.2-1.3 (m,6).

The diacetates **47** *and* **48**. A soln of **45** and **46** (1.12 g; 2.84 mmol) in pyridine (3.5 ml) and Ac_2O (2.14 ml; 22.7 mmol) was stirred at r.t. for 8 hr and finally at 80° for 90 min. The mixture was poured into ice-water and the product isolated with ether. Purification by column chromatography (1:1) yielded a mixture of **47** and **48** (1.10 g; 81%). The same result was obtained on the separate compounds **45** and **46**. **47**: R_f (4:1) 0.50; IR (film) 1746 cm^{-1}; NMR (CCl_4) 7.30 (s,5), 5.42 (t, J = 10.5 Hz, 1), 4.8–4.3 (m,2), 4.47 (s,2), 3.9–3.1 (m,4), 3.58 (s,3), 3.25 (s,3), 2.19 (m,2), 2.0–1.4 (m,6), 1.97 (s,3), 192 (s,3), MS m/z 478 (M^+,0.05), 477 (0.2), 237 (4.5), 220 (20), 91 (100). **48**: R_f (EtOAc) 0.63; NMR 7.35 (s,5), 5.0–4.5 (m,2), 5.24 (t, J = 10.8 Hz, 1), 4.51 (s,2), 4.0–3.2 (m,4), 3.66 (s,3), 3.44 (s,3), 2.5-1.2 (m,6), 2.28 (m,2), 2.06 (s,3), 2.00 (s,3).

The acetates **51** *and* **52**. The benzylethers **47** and **48** (777 mg; 1.63 mmol) in EtOH (15 ml) were hydrogenolized with 10% Pd/C (150 mg) at r.t. After filtration of the catalyst, the filtrate was concentrated *in vacuo* and the residue dissolved in ether. The soln was washed with sat Na_2CO_3 aq. Workup yielded a mixture of **49** and **50** (585 mg; 93%). The same result was obtained on the separate compounds **47** and **48**. **49**: R_f (EtOAc) 0.39; IR (KBr) 3700–3100 cm^{-1}; NMR 5.53 (t, J = 10.2 Hz, 1), 4.77 (dt, J = 10.8, 10.8 and 4.8 Hz,), 4.58 (m,ΣJ = 6.5–7.0 Hz, 1), 4.0–3.2 (m,4), 3.66 (s,3), 3.29 (s,3), 2.32 (m,2), 2.07 (s,3), 2.00 (s,3), 2.00–1.3 (m,6); MS m/z 387 ($M^+ - 1$, 0.35), 373 (0.4), 283 (3), 177 (25), 91 (16), 43 (100). **50**: R_f (EtOAc) 0.44; NMR 5.23 (t, J = 10.5 Hz, 1), 4.76 (dt, J = 11.1, 11.1 and 4.8 Hz, 1), 4.55 (dd, J = 8.4 and 3.3 Hz, 1), 3.70 (s,3), 3.47 (s,3), 4.1–3.2 (m,4), 2.5–1.2 (m,6), 2.30 (m,2), 2.08 (s,3), 2.00 (s,3).

To Collins reagent (1.84 g; 7.12 mmol) in CH_2Cl_2 (40 ml) was added a soln of **49** and **50** (460 mg; 1.19 mmol) in CH_2Cl_2 (23 ml). The mixture was stirred for 15 min at r.t. and then filtered on 7 g

florisil. The filtrate was washed with dil H_2SO_4 and sat Na_2CO_3 aq. Workup yielded the diastereoisomeric aldehydes (345 mg; 75%) sufficiently pure for further use: R_f (ethyl acetate) 0.56. To methyltriphenylphosphonium bromide (2.37 g; 6.64 mmol) in DME (28 ml) was added 1.6 M butyllithium–hexane soln (4.15 ml) at 0°. After 1 hr the suspension was decanted and 8 ml of the supernatant liquid was added dropwise to an ice-cold soln of the aldehydes (427 mg; 1.11 mmol) in DME (15 ml). After stirring for 30 min at 0°, there were added sat NH_4Cl aq (5 ml) and ether (50 ml). Workup and column chromatography (1:1) yielded **51** and **52** (264; 62%): R_f (1:1) 0.31; IR (film) 1740 (bd), 1642 cm^{-1}; NMR 6.2–5.7 (m,1), 5.7–5.1 (m,3), 5.0–4.4 (m,2), 4.0–3.0 (m,2), 3.65 (s,3), 3.41 and 3.27 (2s,3), 2.06, 2.03, 1.99 and 1.97 (4s,6), 2.5–1.4 (m,5), 2.28 (m,2); MS 383 (0.02), 293 (1), 202 (31), 43 (100).

Grieco's lactone **53**. A soln of diastereoisomeric mixture (264 mg; 0.688 mmol) **51** and **52** in acetonitrile (7.5 ml) and 6 N HCl (1.9 ml) was stirred for 2 hr at room temp. The reaction was quenched by ether and the organic phase was washed with a sat Na_2CO_3 aq. The residue obtained after drying ($MgSO_4$) and concentration *in vacuo*, was dissolved in dry benzene (35 ml). After the addition of silver carbonate on celite (4 g; 7 mmol) the mixture was heated for 35 min at reflux. The mixture was cooled, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (ether as eluent) yielding **53** (122 mg; 48%): m.p. 122–123° from CH_2Cl_2–hexane, (Found: 58.2, H, 6.5. $C_{15}H_{24}O_5$ requires: C, 58.7, H, 6.6%); R_f (ether) 0.32; IR (film) 1744 cm^{-1}; NMR (360 MHz, $CDCl_3$) 5.70 (ddd, J = 17.6, 10.9 and 1.0 Hz, 1), 5.33 (d, J = 17.6 Hz, 1), 5.31 (d, J = 10.9 Hz, 1), 5.12 (t, J = 10.5 Hz, 1), 4.92 (dt, J = 11.3, 11.3 and 4.8 Hz, 1), 4.54 (dd, J = 12.3 and 1.0 Hz, 1), 4.38 (dd, J = 12.3 and 2.0 Hz, 1), 3.68 (s,3), 2.62 (dd, J = 18.8 and 7.3 Hz, 2.34 (dd, J = 18.8 and 2.0 Hz, 1), 2.3–1.9 (m,4), 2.10 (s,3), 2.03 (s,3), 1.97 (dd, J = 13.7 and 4.8 Hz, 1), 1.52 (dd, J = 13.7 and 11.3 Hz, 1).

Acknowledgements—We thank the N.F.W.O. and the "Ministerie voor Wetenschapsbeleid" for financial help to the laboratory. F.Z. is indebted to the I.W.O.N.L. for a graduate scolarship.

REFERENCES

[1]S. M. Kupchan, R. J. Hemingway, D. Werner, A. Karim, A. T. McPhail and G. A. Sim, *J. Am. Chem. Soc.* **90**, 3596 (1968).

[2a]P. A. Grieco, M. Nishizawa, S. D. Burke and N. Marinovic, *Ibid.* **98**, 1612 (1976); [b]P. A. Grieco, M. Nishizawa, T. Oguri, S. D. Burke and N. Marinovic, *Ibid.* **99**, 5773 (1977); [c]P. A. Grieco, J. A. Noguez and Y. Masaki, *J. Org. Chem.* **42**, 495 (1977).

[3]J. A. Marshall and D. E. Seite, *Ibid.* **40**, 534 (1975); J. A. Marshall and G. A. Flynn, *Synthetic Commun.* 7, 417 (1977).

[4a]S. Danishefsky, T. Kitahara, P. F. Schuda and S. J. Etheredge, *J. Am. Chem. Soc.* **98**, 3028 (1976); [b]S. Danishefsky, P. F. Schuda, T. Kitahara and S. J. Etheredge, *Ibid.* **99**, 6066 (1977).

[5]P. M. Wege, R. D. Clark and C. H. Heathcock, *J. Org. Chem.* **41**, 3144 (1976).

[6]R. Scheffold, L. Révész, J. Aebersold and A. Schaltegger, *Chimia* **30**, 57 (1976).

[7]M. Isobe, H. Iio, T. Kawai and T. Goto, *J. Am. Chem. Soc.* **100**, 1940 (1978).

[8a]F. Zutterman, P. De Clercq and M. Vandewalle, *Tetrahedron Letters* 3191 (1977); [b]P. De Clercq, *Communication at the 2nd IUPAC Symposium on Organic Synthesis.* Israël (10–15 Sept. 1978).

[9]S. Torii, T. Okamoto and S. Kadono, *Chemistry Letters* 495 (1977).

[10]R. K. Boeckman, Jr., M. Ramaiah and J. B. Medwid, *Tetrahedron Letters* 4485 (1977).

[11a]G. R. Kieczykowski, M. R. Roberts and R. H. Schlessinger, *J. Org. Chem.* **43**, 788 (1978); [b]G. R. Kieczykowski and R. H. Schlessinger, *J. Am. Chem. Soc.* **100**, 1938 (1978).

[12]E. W. Colvin, R. A. Raphael and J. S. Roberts, *Chem. Commun.* 858 (1971).

[13]H. Van Bekkum, C. B. Van den Bosch, G. Van Minnen-Pathuis, J. C. De Mos and A. M. Van Wijk, *Recueil* **90**, 137 (1971).

[14]R. Tang and K. Mislow, *J. Am. Chem. Soc.* **92**, 2100 (1970); D. A. Evans, G. C. Andrews and C. L. Sims, *Ibid.* **93**, 4956 (1971).

[15]G. B. Payne, *Tetrahedron* **18**, 763 (1962).

[16]R. B. Woodward, J. Gosteli, I. Ernest, R. J. Friary, G. Nestler, H. Raman, R. Sitrin, Ch. Sutter and J. K. Whitesell, *J. Am. Chem. Soc.* **95**, 6853 (1973).

[17]H. B. Henbest and R. A. Wilson, *J. Chem. Soc.* 1958 (1957).

[18]K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.* **95**, 6136 (1973).

[19]M. Santelli and J. Viaha, *Tetrahedron* **34**, 2327 (1978); Reported by Prof. Grieco at the 7th Workshop Conference Hoechst (24–27 Sept. 1978).

[20]P. L. Creger, *J. Org. Chem.* **37**, 1907 (1972); S. Danishefsky, M. Y. Tsai and T. Kitahara, *J. Org. Chem.* **42**, 394 (1977).

[21]C. G. Chavolarian, S. L. Woo, R. D. Clark and C. Heathcock, *Tetrahedron Letters* 1769 (1976); W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.* **94**, 4780 (1972).

[22]M. Fetizon and M. Golfier, *C. R. Acad. Sci.* (C), 900 (1968).