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A General Method for the Synthesis of Clerodane Diterpenoids. Stereospecific Total Syntheses of (±)-15,16-Epoxy-cis-cleroda-3,13(16),14-triene and (±)-Maingayic Acid[1,2]

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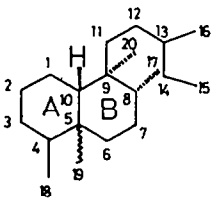
Abstract: A general method for the syntheses of cis- and trans-clerodane diterpenoids has been developed and its applications to the total syntheses of both representatives **11** and maingayic acid (**32**) in racemic forms are described. The common Δ^4-3-octalone intermediates **2a** and **2b** were prepared from 3,4-dimethyl-2-cyclohexenone by a stereospecific conjugate addition-alkylation sequence and the subsequent thermodynamically controlled annelation. The dimethylcuprate addition to **2a** followed by enolate trapping afforded stereospecifically the cis-alcohol **12**, from which (±)-**11** has been synthesized. On the other hand hydrocyanation of **2b** gave trans-intermediate **33**, and then it has been converted to (±)-maingayic acid (**32**).

Clerodane diterpenoids are a class of the bicyclic compounds with the basic skeleton **1**, which are formed biogenetically by the backbone rearrangement of labdadienyl cation produced by the cyclization of geranylgeranyl pyrophosphate.[3] Since the structure determination of columbin, the first member, in 1956,[4] clerodane diterpenes have been found in increasing numbers[5] mainly as the constituents of higher plants and also from microorganisms,[6] and marine animals.[7] A variety of biological activities such as antibiotic,[8,9] antifeedant,[10] antitumor,[6,11] piscicidal,[12,13] psychotropic[14] and others[9,15] have been known for this class of natural products.

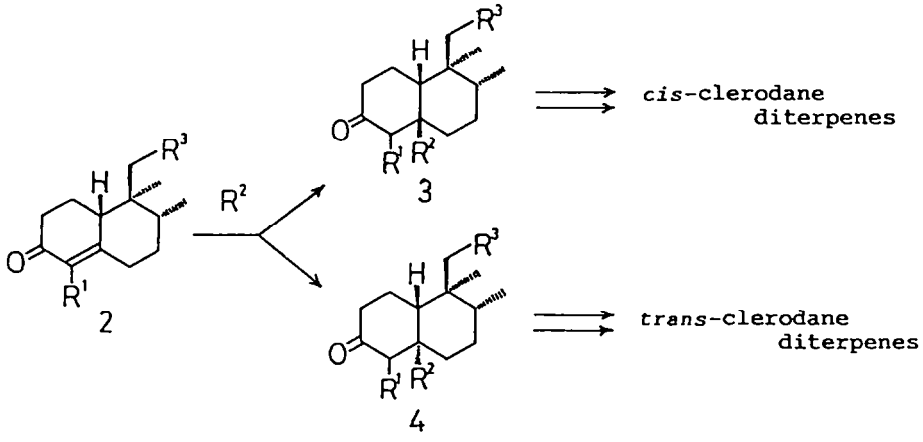


1 A/B: *trans* or *cis*

The synthetic aspects of clerodane diterpenoids had remained unexplored rather until recently. In connection with the total synthesis of the related diterpene, portulal,[16c] we reported a stereospecific approach to clerodane diterpenoids by the use of Diels-Alder protocol in 1973.[16a] Then a nonstereoselective total synthesis of annonene, a trans-clerodane diterpene, appeared.[17] Synthetic efforts thereafter were directed mainly to the compounds with antifeedant activity,[18,19] which are structurally featured by the presence of a hydroxyl group at C-6, and three total syntheses have been achieved for ajugarins I[20,21] and IV.[22] On the other hand only limited numbers of the synthetic works have been published on the more common types of clerodane diterpenoids.[16,23-25] In this paper we delineate in full detail a general and efficient method for the syntheses of both cis- and trans-clerodane diterpenoids and the demonstration of its utility by the total syntheses of representatives for both types. Prior to the discussion of the synthetic plan it

would be pertinent to survey the major structural variations of clerodane diterpenoids:[26] (i) they are divided into two major groups, cis and trans, with respects to the ring fusion, the latter being more prevailing, (ii) the vicinal dimethyl groups at C-8 and C-9 are usually cis, but trans in rare cases for both major groups,[6,12b] (iii) an olefinic bond exists commonly between C-3 and C-4, its presence linking biogenetically with the backbone rearrangement, (iv) there are variations in the site of oxygenation on the rings, e.g. C-1 and C-2 for psychotropic divonorin A[14] or C-6 for antifeedant clerodanes,[10] (v) C-17 ∿ C-19 could be the substituents of various oxidation levels, (vi) the six-carbon side chain has functionality of all sorts, most frequently with 3-furyl, 5(2H)-furanon-2-yl or 3-carboxy-2-propen-2-yl termini. In this work we have aimed at the synthetic method for rather basic and more common type of clerodane diterpenoids which will find utilization in the widest possible range.

In the design of the synthetic path the stereospecific device for the constructioin of the four contiguous diastereomeric centers at C-5, C-8, C-9, and C-10 would be central. Our basic strategy to meet this problem is as depicted in Scheme 1. The Δ^4-octal-3-one derivative 2 with the requisite stereochemical



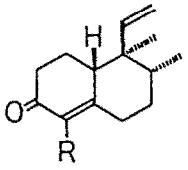
Scheme 1

relationship at C-8, C-9, and C-10[27] is selected as the key intermediate, and the stereoselective constructions of cis and trans clerodane skeletons are envisaged from the common intermediate by the conjugate addition of C_1 synthon with proper choice of the reagents and/or reaction conditions. When we start from the intermediate 2a without substituent at C-4, conjugate addition-alkylation protocol[28] may be expedient for the introduction of the substituents at C-4 and C-5 at the same time. R^1 and R^2 could be the C_1-synthon of various oxidation states and in this way the method should be generally applicable to the syntheses of both cis and trans clerodane diterpenoids with cis-8,9-dimethyl groups.

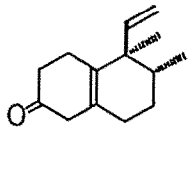
Results and Discussion

Preparation of the common octalone intermediates 2. For the synthesis of the Δ^4-octal-3-one intermediate by Robinson type annelation, the stereoselective preparation of 3,3,4-trisubstituted cyclohexanone derivative like 5 and its regioselective enolate formation become mandatory. An expedient solution of both

problems at the same time is conjugate addition-alkylation procedure,[28] provided that the introduction of the first alkyl synthon to 3,4-dimethyl-2-cyclohexenone (6) is stereoselective in the desired sense - i.e. trans to the 4-methyl group. Fortunately in this respect we could utilize straightforwardly the result of F. Ziegler[29] that the conjugate addition of lithium divinylcuprate-tri-n-butylphosphine complex to 6 afforded stereospecifically[30] the vinylated product 7. If the kinetic enolate formed in this reaction is trapped by a suitable electrophile and then the annelation is performed, the Δ^4-octal-3-one intermediate 2 with the desired configuration at C-8 and C-9 will be obtained, the vinyl group making further side chain manipulation possible. With respect to the stereochemistry at the ring junction (C-10) we anticipitated the thermodynamic control which would be favorable for the trans relationship between the C-8 methyl group and the C-10 hydrogen atom, since otherwise the 1,3-diaxial nonbonded interaction between them impart energetic disadvantage, even if the difference of C-9 groups in bulkiness might not be decisive.



2a R = H
2b R = Me



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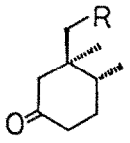

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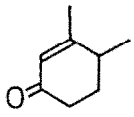

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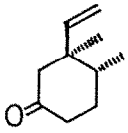

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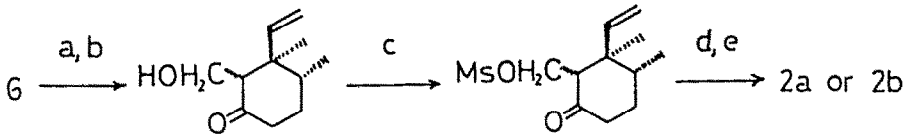
The synthesis started from the conjugate addition of 3,4-dimethyl-2-cyclohexenone (6) with vinylmagnesium bromide-Cu(I)-tri-n-butylphosphine complex[31] in place of divinyl copper lithium system[29] and subsequent capture of the intermediary enolate with formaldehyde. When the cuprate addition reaction was conducted in tetrahydrofuran (THF) at -70 ∿ -20 °C over several hours followed by the introduction of gaseous formaldehyde, the hydroxy ketone 8 was obtained as a



8 9

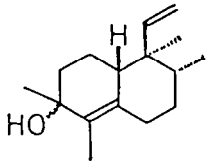
Scheme 2. Reagents: CH_2=CHMgBr, CuI•n-Bu_3P, THF; (b) CH_2O; (c) MsCl, Et_3N, CH_2Cl_2; (d) $CH_3COCH_2CO_2Me$ or $CH_3CH_2COCH_2CO_2Me$, MeONa, MeOH, benzene, Δ; (e) 2M HCl, MeOH, Δ

diastereomeric mixture of approximately equal amounts in 40 ∿ 70% yield depending upon the scale of the reaction.[32] The use of the cuprate ligand other than tri-n-butylphosphine - e.g. dimethyl sulfide - somewhat lowers the yield of **8**. Although the separation of the diastereomers was not attempted, the assignment of ^{1}H NMR data for each was possible (cf. Experimental). The derived labile mesylate **9**[33] was allowed to react with methyl acetoacetate or methyl 3-oxopentanoate in the presence of sodium methoxide. After treatment with hydrochloric acid under refluxing, the desired bicyclic enones **2a** and **2b** were produced in the overall yields of 70 ∿ 80%. In the case of **2a** the deconjugated enone **10** also formed in considerable amounts (10 ∿ 15%), but the latter could be removed readily by silica gel chromatography. The spectroscopic data were in conformity with their formulation as Δ^4-octalone derivatives. Especially even in ^{13}C NMR spectra no sign for the presence of the respective diastereomers was detected in both cases(**2a** and **2b**). Thus the annelation reaction was stereospecific and in view of the thermodynamic stability as assumed above the desired stereochemical relationship at the three diastereomeric carbon atoms in **2** would reasonably assigned, though the ultimate confirmation of this was postponed till the completion of the total syntheses of natural products.

Total synthesis of 15,16-epoxy-cis-cleroda-3,13(16),14-triene, the representative of cis-clerodane diterpene. As a target of natural cis-clerodane diterpenoids we selected the furanoid compound **11**, a representative with a typical and the simplest functionality. It was isolated as a constituent of Solidago arguta Ait. and the structure assigned[34] have been confirmed by the X-ray crystallographic analysis of a related compound.[35] The central roles of **11** in the chemistry of clerodane diterpenoids are illustrated by the chemical correlation with both cis[36] and trans[37,38] compounds.

For the introduction of a cis-methyl group to the C-5 position of the key intermediate **2**, we took advantage of the well-documented fact that the conjugate addition of organometallic species to Δ^4-octal-3-one occurs from the less-hindered convex side, giving the cis-decalone.[39] Firstly we investigated the reaction of dimethylcopper lithium with the more convergent precursor **2b**. Although a variety of conditions and modifications were examined with respect to the reagent preparation[39-41](i.e. methyllithium solutions of various sources, usual or low halide, and cuprous salts such as CuI,[42] CuCN[43] or CuBr·Me_2S,[44] and the ratios of both,[43b] and the solvent, diethyl ether and this mixed with dimethyl sulfide or pentane[45]), the reaction was elusive and mostly resulted in the formation of 1,2-adduct **24**. In some favorable cases under House's condition (MeLi-CuBr/ether- pentane)[45] the desired 1,4-adduct **26** (< 10%) was obtained, but the result was not always reproducible.[46] The reaction at the presence of Lewis acids, which is known to be effective for the conjugate addition to hindered ketone,[47] also failed to afford the 1,4-adduct and resulted mostly in the formation of diene **25** derived from the 1,2-adduct **24** by dehydration. With the concept of electron transfer mechanism[48] H. O. House has determined the correlation between reduction electrode potential and the reactivity of α,β-unsaturated ketones in the lithium organocuprate addition and counted the increment values for the substituents.[45] By the use of these correlation the reduction potential for **2b** is estimated to be -2.2 V, a value near to the threshold (E_{red} -2.4 V) for the addition to occur. The steric hindrance would be undoubtedly the additional factor to retard the reaction of **2b** with the

cuprate reagent. Interestingly the application of the recently advocated procedure using trimethylsilyl chloride as an addend[49-51] did give reproducibly the 1,4-adduct **26** though still in low yield (∿ 18%). Accordingly we turned to investigate the cuprate addition to more reactive substrate **2a** (E_{red} -2.1 V) and subsequent methylation of the so-formed enolate.[28] The reaction of **2a** with dimethylcopper lithium in ether(-10 ∿ -0 °C) followed by treatment with methyl iodide after the exchange of the solvent with dimethoxyethane(DME)[52] gave a complex mixture of mono- and dimethylated products, from which the compound **27** derived from the isomerized enolate was obtained as the major product. It was characterized by the ^{1}H NMR spectrum which exhibited methyl singlets at δ 0.89 and 1.14, methyl doublets at δ 0.79 and 0.99, and doublets of the AX type signal at δ 1.79 and 2.83 (J = 16 Hz) due to the methylene group at C-4. The conversion of the intermediary enolate to stannyl species prior to the methylation[53] was ineffective to improve the situation. Thus a remaining choice was the cuprate reaction of **2a** and the subsequent trapping of the enolate by more reactive electrophile. When the reaction mixture of **2a** with dimethylcopper lithium in a mixture of diethyl ether and pentane at -20 °C was treated with gaseous formaldehyde, keto alcohol **12** was obtained as the single diastereoisomer in 46% yield. The stereochemistry as **12a** is assumed on the basis of the comformational analysis as for **26**.[46]



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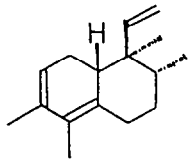

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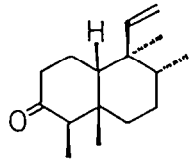

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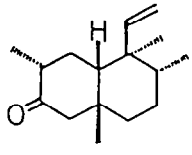

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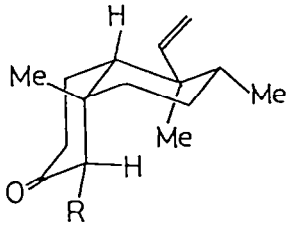
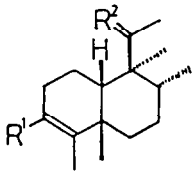
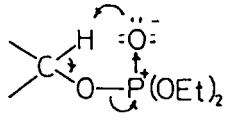


12a R = CH_2OH
26a R = Me



28 R^1 = H; R^2 = H,OH
29 R^1 = $OP(OEt)_2$; R^2 = H, OH
30 R^1 = $OP(OEt)_2$; R^2 = O



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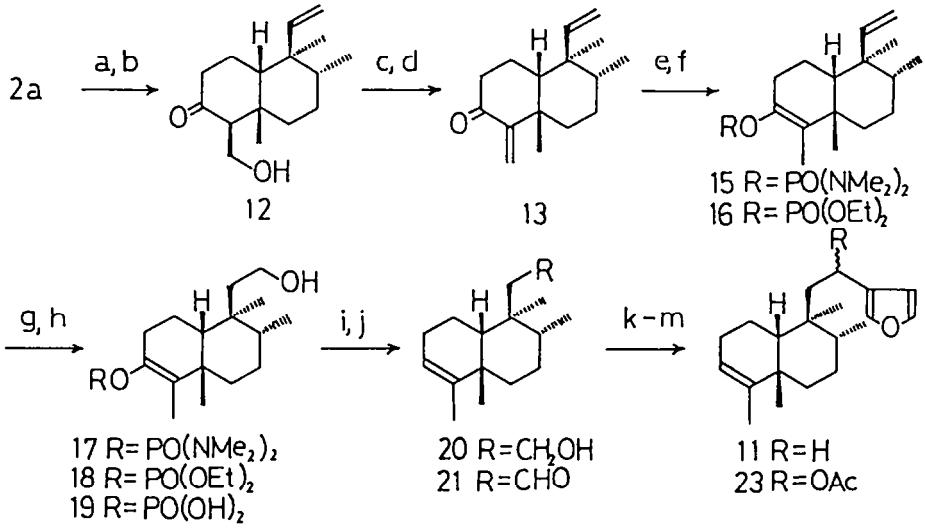
For completion of the synthesis of **11** from **12**, we needed the conversion of 3-keto-18-ol structure to $\Delta^{3,4}$-4-methyl system and the appendage of β-furyl group in the side chain. These transformation have been achieved efficiently as shown in Scheme 3. First the dehydration of **12** afforded methylene ketone **13** in 80% yield.

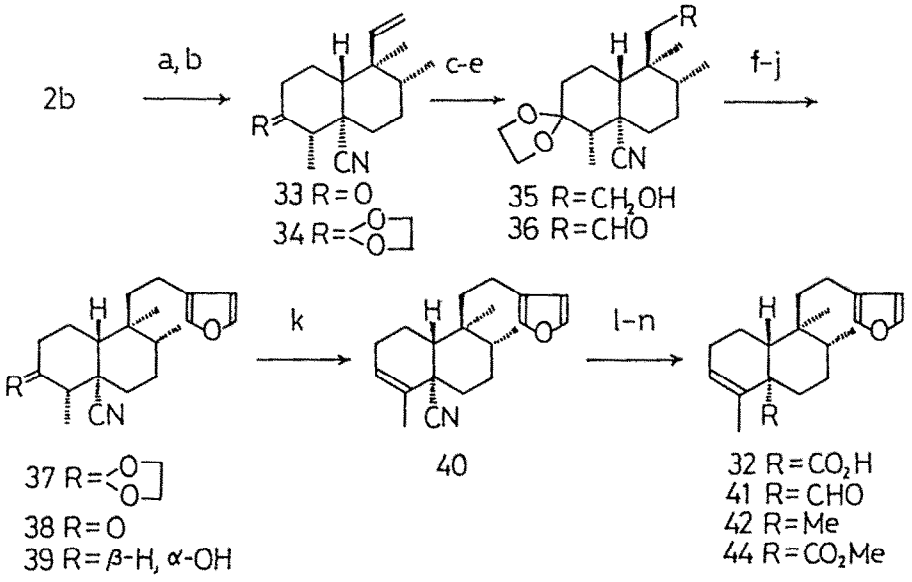
Conjugate hydride addition of **13** with lithium tri-sec-butylborohydride (L-Selectride ®)[54] afforded the ketone **26** obtained above by the dimethylcuprate addition to **2b**. On the other hand trapping of the reduction intermediate with bis(dimethylamino)phosphorochloridate furnished enol phosphate ester **15** in 51% yield. It was chemo- and regioselectively hydroborated with thexyl borane and then oxidized to yield the alcohol **17**. Removal of the phosphate group from **17** by Birch reduction produced the subgoal substance **20** in 56.4% overall yield from **15**. When the hydroboration of **15** was conducted with diborane and processed as above, the secondary alcohol **28** formed in a considerable amount (17% yield vs. 41% of **20**), a puzzling result in views of rather sterically congested environment of the C-11 sp^2 carbon atom and the absence of a neighboring influencial polar group.[55] Moreover the enol phosphate **16**, obtained from **13** in the same way as **15** through the reduction and trapping with diethylphosphorochloridate afforded, after the hydroboration-oxidation, three products, **18**, **29**, and **30** in 53%, 12%, and 11% yields respectively. The formation of the ketone **30** is worthy to note and might be explained by the phosphate group transfer to the secondary hydroxyl group formed and ensuing oxidative fragmentation as in **31**. Reductive conversion of **18** to **20** with lithium-ethylamine was unsuccessful since the ester group in **18** was labile under the reaction condition used and the very polar product, presumably **19** formed. The



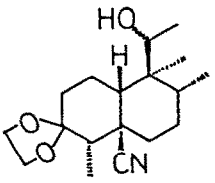
Scheme 3. Reagents: (a) Me_2CuLi, Et_2O-pentane, -20 °C; (b) CH_2O; (c) MsCl, Et_3N, CH_2Cl_2; (d) DBU; (e) $LiB(CHMeEt)_3H$, THF, -78 °C; (f) $(Me_2N)_2POCl$, HMPA; (g) $Me_2CHCMe_2BH_2$, THF; (h) H_2O_2, NaOH; (i) Li, $EtNH_2$, t-BuOH; (j) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (k) 3-furyllithium, Et_2O; (l) Ac_2O, pyridine; (m) Li, liq NH_3, -78 °C

transformation of **20** to **11** proceeded in a usual way.[16c] The aldehyde **21** obtained by the Swern oxidation of **20** was allowed to react with β-furyllithium and the product was acetylated. The resulting acetate **23** was treated with lithium in liquid ammonia to afford the target compound **11**. The IR and ^1H NMR spectra of the synthetic product were superimposable with those[56] of the natural product. This result represents the first total synthesis of racemic cis-clerodane diterpenoid and at the same time confirms the stereochemistry of the key octalone intermediate **2a**.

Total synthesis of (±)-maingayic acid (32), the representative of trans-clerodane diterpenes. The feasibility of our method in the synthesis of trans-clerodane diterpenoids was tested on an access to maingayic acid (**32**).[13] This compound, featured by the presence of a carboxyl group at trans-angular position and β-furyl side chain, isolated from the leaves of Callicarpa candicans (Burm. f.) Hochr. (Verbenaceae), which has been used to stupefy fishes in Caroline and Philippine Islands. It has a piscicidal activity as strong as 15% of pentachlorophenol.[13] For the stereospecific introduction of a functionalized C_1-synthon to the octalone intermediate **2** in a trans manner, the hydrocyanation protocol by Nagata's reagent[57] is an obvious candidate, since the reaction of Δ^4-octal-3-one without the methyl group at C-10 is known to give predominantly the trans product both in kinetic and thermodynamic conditions. Moreover the presence of 9α-methyl in **2** would disfavor additionally the formation of of cis-product by its severe nonbonded interaction with C-4 carbon atom in the steroidal-like transition state.[57] Treatment of **2b** with diethylaluminum cyanide in benzene at room temperature for 2 h afforded cyanoketone **33** in high yield. The trans structure of the product **33** was supported by the appearance of the tertiary methyl proton signal in the ^1H NMR spectrum at the position deshielded by 0.23 ppm as compared with that of the starting material **2b**, when the diamagnetic anisotropic effect caused by the cyano group in 1,3-diaxial relationship[58] was taken into consideration. After the protection of the keto group the cyanoketone **33** was hydroborated with diborane and the product was oxidized. In this way the desired primary alcohol **35** was obtained in 56% yield,



Scheme 4. Reagents: (a) Et_2AlCN, benzene-toluene, 28-35 °C; (b) ethylene glycol, TsOH, benzene; (c) B_2H_6, THF; (d) H_2O_2, NaOH; (e) CrO_3, pyridine, CH_2Cl_2; (f) 3-furyllithium, Et_2O; (g) Ac_2O, pyridine, (h) Li, liq NH_3, -78 °C; (i) 2M HCl, Me_2CO; (j) $LiB(CHMeEt)_3H$, THF, -78 °C; (k) $POCl_3$, pyridine; (l) i-Bu_2AlH, toluene, 0 °C; (m) AcOH, THF, H_2O; (n) $NaClO_2$, NaH_2PO_4, t-BuOH, H_2O, $Me_2C{=}CHMe$



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again being accompanied by a considerable amount of secondary alcohol **43** (24% yield). The alcohol **35** was converted by Collins oxidation to the aldehyde **36** (75.5% yield) which gave the β-furyl compound **38** in 64% yield by the same procedure as above (**21** → **11**) and subsequent deprotection. The remaining synthetic task was the transformations of the 3-keto group to $\Delta^{3,4}$-double bond and of the angular cyano group to a carboxyl group. Reduction of **38** with L-Selectride ® yielded the α-axial alcohol **39**, which was dehydrated to furnish the olefinic compound **40** in 70% yield. The cyano group in **40** was converted to an aldehyde through reduction with diisobutylaluminum hydride (DIBAL) followed by hydrolysis, giving (±)-**41** in high yield(94%). The IR and ^{1}H NMR data of (±)-**41** showed a good agreement with those[59,60] of the aldehyde derived from maingayic acid. This aldehyde has been converted to annonene **42**, which is the constituent of *Annona coriacea*[61] and *Solidago serotina* Ait.[62] Therefore the production of (±)-**41** signify the formal total synthesis of annonene (±)-**42**[17] and also verify the assumption for the *trans*-stereochemistry of the angular substituent appended by hydrocyanation.

Finally the oxidation of the aldehyde to a carboxyl group needed some scrutinization of the procedure, since standard methods like chromium trioxide or silver oxide oxidation failed to effect the desired transformation. Eventually the target compound (±)-**32** was obtained by Lindgren-Nilsson procedure with sodium chlorite[63] in 21% yield(35% based on the converted material). The identity of the racemic synthetic product with maingayic acid **32**[64] has been confirmed by the comparison of IR and ^{1}H NMR spectra of the corresponding methyl esters **44**.

Conclusions

A general stereospecific method for the synthesis of both *cis*- and *trans*-clerodane diterpenoids have been developed firstly. In this method the easily prepared Δ^4-octal-3-one derivatives **2** were used as the common key intermediate and the angular substituents could be introduced by conjugate addition. Thus the steric mode (*cis* or *trans*) and the functionality of the substituent could be optional in view of a variety of the conjugate addition reactions. These possibilities have been demonstrated by the stereospecific syntheses of (±)-**11** and (±)-maingayic acid **32**, *cis*- and *trans*-clerodane diterpenoids respectively. Furthermore we have recently extended this method to the asymmetric synthesis of both *neo*- and *ent*-*neo*-clerodane diterpenoids.[65] Accordingly our method will be useful for the synthesis of clerodane diterpenoids with a wide variety of stereostructures and should be valuable for the purpose of the confirmation of their structures as well as the access to the biologically active substances.

Experimental Section

Melting points were determined on a Yanagimoto micro hot-stage appratus MP-S2 and are uncorrected. IR spectra were recorded on a JASCO A-100 spectrometer. ^{1}H NMR spectra were taken on a JEOL PS-100, R-90H or GX-400 spectrometers and ^{13}C NMR spectra on a JEOL FX-100 spectrometer, in $CDCl_3$ relative to tetramethylsilane as an internal standard. High resolution mass spectra were measured on a JEOL D-300 spectrometer. Microanalyses were performed at the microanalytical laboratory,

Faculty of Science, Osaka City University. Preparative TLC was performed on 20 x 20 cm glass plates coated with Merck Silica Gel 60 PF-254 (Art No. 7747) or precoated plates with a thickness of 0.5 mm(Art no. 5744). Reagents and solvents were used as purchased or purified as follows: ether and tetrahydrofuran(THF) were distilled from $LiAlH_4$ or sodium/benzophenone immediately before use. Dimethylformamide(DMF) and dimethyl sulfoxide(DMSO) were distilled from calcium hydride. When dealing with air and moisture sensitive compounds reactions were run in a flame-dried flask under a positive pressure of argon or nitrogen gas. Extract solutions were dried with anhyd magnesium sulfate before the solvent evaporation.

(±)-2-Hydroxymethyl-3α,4α-dimethyl-3β-vinylcyclohexanone (8). A solution of tetrakis-[iodo(tri-n-butylphosphine)copper] was prepared by addition of tri-n-butylphosphine (12.5 mL, 0.05 mol) to a suspension of CuI (9.5 g, 0.05 mol) in anhyd ether (100 mL) at 0 °C and stirring of the mixture at room temp until a clear solution resulted. To this solution was added a vinylmagnesium bromide solution, prepared from vinyl bromide (7 mL, 0.1 mol) and Mg (2.43 g, 0.1 mol) in THF (20 mL) and diluted with THF (40 mL), dropwise at -78 °C during 1 h and the reaction mixture was stirred for further 15 min. To the vinylcuprate solution thus formed was added dropwise a solution of 3,4-dimethyl-2-cyclohexenone[66] (4.9 g, 0.04 mol) in THF (20 mL) at - 78 °C over 30 min and the temperature of the mixture allowed to raise gradually to -40 °C during 1.5 h. An excess of formaldehyde gas, formed by the pyrolysis of paraformaldehyde at ∿ 170 °C, was introduced by means of nitrogen flow over 4 h at -50∿-40 °C and the mixture was allowed to warm up to -10 °C during 30 min. Then it was poured onto saturated NH_4Cl-ice and the product was extracted by ether (x 3). The combined ether layers were washed with brine and dried. The residue left after evaporation of the solvent was purified by chromatography (SiO_2, 5:1-2:1 n-hexane-EtOAc), giving the alcohol **8**, 4.73 g (65.8%) as a colorless oil, bp 114-116 °C (0.15 mmHg): IR(neat) 3400, 3070, 1710, 1630, 910 cm^{-1}. HRMS Calcd for $C_{11}H_{18}O_2$: 182.1307. Found: 182.1312. Assignments of ^1H NMR data for the diastereomers were possible with reference to the spectrum of a partially separated mixture: **8a** 1.12 (s, 3H), 1.12 (d, J = 7 Hz, 3H), 3.58(dd, J = 4,12 Hz, 1H, broad unresolved signal without D_2O addition), 3.95 (dd, J = 9.5,12 Hz, 1H, broad without D_2O addition), 4.94 (dd, J = 1.5,17 Hz, 1H), 5.00 (dd, J = 1.5, 11 Hz, 1H), 5.72 (dd, J = 11,17 Hz, 1H); **8b** 0.77 (s, 3H), 0.84 (d, J = 7 Hz, 3H), 3.45 (dd, J = 4,12 Hz, 1H, broad without D_2O addition), 3.90 (dd, J = 9,12 Hz, 1H, broad without D_2O addition), 4.92 (dd, J = 1.5,17 Hz, 1H), 5.18 (dd, J = 1.5,11 Hz, 1H), 5,78 (dd, J = 11,17 Hz, 1H).

(±)-2-Mesyloxymethyl-3α,4α-dimethyl-3β-vinylcyclohexanone (9). Mesyl chloride (4.8 g, 42 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a mixture of the alcohol **8** (6.56 g, 36 mmol) and triethylamine (5.33 g, 52 mmol) in CH_2Cl_2 (100 mL) at -10∿0 °C and the reaction mixture was kept at 0 °C for 1 h, then poured onto ice-water. The water layer was extracted with CH_2Cl_2 and the combined organic layers were washed successively with 2M HCl, saturated $NaHCO_3$ and brine. The dried solution was carefully concentrated in vacuo and passed through a column of silica gel (99:1 CH_2Cl_2-MeOH), giving the unstable mesylate **9** as a diastereomeric mixture, an oil, 8.29 g (93%): IR(neat) 3080, 1715, 1635, 1170, 955, 832, 730 cm^{-1}; ^1H NMR(CCl_4) **9a**: 1.19(d, J = 7 Hz, 3H), 1.21 (s, 3H), 3.02 (s, 3H), 4.12 (dd, J = 4,10 Hz, 1H), 4.57 (t, J = 10 Hz, 1H), 5.09 (dd, J = 1.5,17 Hz, 1H), 5.17(dd, J = 1.5,11 Hz, 1H), 5.79 (dd, J = 11,17 Hz, 1H); **9b**: 0.73(s, 3H), 0.87(d, J = 7 Hz, 3H), 3.98 (dd, J = 2,10 Hz, 1H), 4.48 (t, J = 10 Hz, 1H), 5.09 (dd, J = 1.5,17 Hz, 1H), 5.32 (dd, J = 1.5,11 Hz, 1H), 5.88 (dd, J = 11,17 Hz, 1H).

(±)-4,4aβ,5,6,7,8-Hexahydro-5α,6α-dimethyl-5β-vinyl-2(3H)-naphthalenone (2a). To a solution of methyl acetoacetate (15 mL, 140 mmol) in a mixture of dry benzene (60 mL) and anhyd MeOH (60 mL) was added NaOMe solution in MeOH (from Na, 7.5 g, 0.324 mol atom, and MeOH, 375 mL) under stirring at room temp, followed by the dropwise addition of the mesylate **9** (15.5 g, 59.6 mmol) dissolved in dry benzene (100 mL) during 30 min. After the mixture was allowed to react at room temp for 3.5 h under stirring, the reaction was quenched by the addition of 2M HCl (100 mL) and the MeOH was evaporated in vacuo. The crude product, obtained by ether extraction and evaporation of the solvent, was dissolved in MeOH (150 mL) and treated with 2M HCl (100 mL) under refluxing for 5 h. After removal of most of the MeOH, reaction mixture was extracted with ether and the combined ether layers were washed with saturated $NaHCO_3$ and brine. The solvent was evaporated and the residue was chromatographed on a column of silica gel with 6:1 n-hexane-ether. Following the forerun of **(±)-3,4,5,6,7,8-hexahydro-5α,6α-dimethyl-5β-vinyl-2(1H)-naphthalenone (10)**, 2.35 g (13%): IR(neat) 3080, 1727, 1635, 1005, 915 cm^{-1}; ^1H NMR 0.82(d, J = 6 Hz, 3H), 0.97 (s, 3H), 2.74 (s, 2H), 4.92 (dd, J = 2,17 Hz, 1H), 5.05 (dd, J = 2,11 Hz, 1H), 5.53 (dd, J = 11,17 Hz, 1H), the bicyclic enone **2a** was obtained as an oil (12.5 g, 69%): IR(neat) 3080, 1680, 1620, 910 cm^{-1}; ^1H NMR 0.81 (d, J = 7 Hz, 3H), 0.82 (s, 3H), 5.03 (dd, J = 2,17 Hz, 1H), 5.12 (dd, J = 2,11 Hz, 1H), 5.36 (dd, J = 11,17 Hz, 1H), 5.95 (br s, 1H). HRMS, calcd for $C_{14}H_{20}O$: 204.1514. Found 204.1517.

(±)-4,4aβ,5,6,7,8-Hexahydro-1,5α,6α-trimethyl-5β-vinyl-2(3H)-naphthalenone (2b). A solution of methyl 3-oxopentanoate (10.55 g, 81.1 mmol) in a mixture of benzene (25 mL) and MeOH (25 mL) was mixed with NaOMe-MeOH solution (6.42 g, 119 mmol in 150 mL) and the mixture was stirred for 30 min at room temp. To this was added a solution of the mesylate **9** (13.26 g, 51 mmol) in benzene (150 mL). After the stirring at room temp for 15 h and at 40-50 °C for 3 h, the reaction mixture was acidified with 2M HCl and the product was extracted. The obtained oil, dissolved in MeOH (200 mL), was heated with 2M HCl (200 mL) under refluxing for 7 h and worked up as above. The crude product thus obtained was purified by chromatography (SiO_2, 19:1 benzene-EtOAc) to give the bicyclic enone **2b** as an oil (8.76 g, 78.8 %): IR(neat) 3080, 1665, 1635, 1620, 910 cm^{-1}; ^1H NMR(CCl_4) 0.80 (d, J = 6 Hz, 3H), 0.81 (s, 3H), 1.74 (s, 3H), 4.92 (dd, J = 1.5,17 Hz, 1H), 5.10 (dd, J = 1.5,11 Hz, 1H), 5.55 (dd, J = 11,17 Hz, 1H). HRMS, calcd for $C_{15}H_{22}O$: 218.1671. Found 218.1678.

(±)-3,4,4aβ,5,6,7,8,8a-Octahydro-1β-hydroxymethyl-5α,6α,8aβ-trimethyl-5β-vinyl-2(1H)-naphthalenone (12) To a suspension of $Me_2S{\cdot}CuBr$ (3.02 g, 14.7 mmol) in anhyd ether (12 mL) was added 1.6 M MeLi solution (Alpha Chem., low halide, 15.5 mL, 24.8 mmol) at 0 °C over 20 min. Dry pentane (40 mL) was added to the resulting colorless clear solution, when white precipitates formed. The mixture was cooled to -25 °C and the bicyclic enone **2a** (1.00 g, 4.9 mmol) dissolved in anhyd ether (5 mL) was added dropwise under stirring for 30 min. The yellow colored suspension was stirred at the same temp for 1.5 h, followed by the introduction of gaseous formaldehyde for 30 min. The mixture was allowed to warm and poured onto saturated NH_4Cl. Insoluble material was removed by filteration and the filterate was extracted with ether and the ether extract was washed successively with saturated NH_4Cl, saturated $NaHCO_3$ and brine. Crude product obtained by evaporation of the solvent was purified by silica gel chromatography (4:1 hexane-EtOAc) to give β-keto alcohol **12** as single isomer, an oil (570 mg, 46%): IR($CHCl_3$) 3560, 3080, 1695, 1635, 920 cm^{-1}; ^1H NMR 0.80 (d, 5.6 Hz, 3H), 0.88 (s, 3H), 1.18 (s, 3H), 3.07 (dd, J = 3.4,9 Hz, 1H), 3.66 (dd, J = 3.4,11.2 Hz, 1H), 3.94 (dd, J = 9,11.2 Hz, 1H), 4.99 (dd, J = 2,17 Hz, 1H), 5.15 (dd, J = 2,10 Hz, 1H), 5.48 (dd, J = 10,17 Hz, 1H).

(±)-3,4,4aβ,5,6,7,8,8a-Octahydro-5α,6α,8aβ-trimethyl-1-methylene-5β-vinyl-2(1H)-naphthalenone (13). To a solution of the β-keto alcohol **12** (1.60 g, 6.39 mmol) and triethylamine (2 mL) was added dropwise mesyl chloride (0.9 mL, 11.6 mmol) at 0 °C and the mixture was stirred at ambient temp for 2 h. It was poured onto ice-water and the product was isolaterd in a usual manner to give the mesylate as a crystalline solid (ca. 2.5 g). This was dissolved in THF (80 mL) and 1,8-diazabicyclo[4.4.0]undec-7-ene (DBU, 1.6 mL, 10.7 mmol) was added at 0 °C, then the mixture was refluxed for 12 h. After concentration *in vacuo* and acidification with 2M HCl the product was extracted with ether and the extract solution was washed with saturated $NaHCO_3$ and brine, then dried. The crude product was chromatographed (SiO_2, 9:1 hexane- ether) to give the methylene ketone **13** as an oil (1.191 g, 80.1%): IR(CCl_4) 3080, 1690, 1605, 942, 916 cm^{-1}; ^1H NMR 0.71 (d, J = 6 Hz, 3H), 0.81 (s, 3H), 1.13 (s, 3H), 4.90 (dd, J = 1.7, 16.5 Hz, 1H), 5.08 (dd, J = 1.7,10.3 Hz, 1H), 5.25 (br s, 1H), 5.40 (dd, J = 10.3, 16.5, 1H), 6.01 (br s, 1H).

(±)-3,4,4aβ,5,6,7,8,8a-Octahydro-1β,5α,6α,8aβ-tetramethyl-5β-vinyl-2(1H)-naphthalenone (26). A. By reduction of 13 with L-Selectride. To a solution of the methylene ketone **13** (370 mg, 1.59 mmol) in THF (12 mL) cooled at -78 °C was added 1M solution of L-Selectride ® in THF (1.8 mL, 1.8 mmol) and the mixture was stirred at this temp for 2 h. Then the reaction mixture was treated with 30% H_2O_2 (10 mL) and 2M NaOH (30 mL) at room temp for 1.5 h. Ether extraction was followed by washing with $NaHSO_3$ and brine, and the solvent was evaporated. The crude product was purified by silica gel chromatography (19:1 hexane-EtOAc) to afford **26** as crystals (273 mg, 73%), mp 58-59 °C: IR($CHCl_3$) 1700, 1630, 1000, 907 cm^{-1}; ^1H NMR 0.79(d, J 6.2 Hz, 3H), 0.81 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.18 (s, 3H), 2.95 (q, J = 6.8 Hz, 1H), 4.95 (dd, J = 2,17 Hz, 1H), 5.09 (dd, J = 2,11 Hz, 1H), 5.47 (dd, J = 11,17 Hz, 1H). HRMS, calcd for $C_{16}H_{26}O$: 234.1984. Found 234.1985.

B. By dimethylcuprate addition to 2b. To a solution of lithium dimethylcuprate prepared from $Me_2S{\cdot}CuBr$ (3.08 g, 15 mmol) in pentane (70 mL) and ether (12 mL) and 1.8 M methyllithium solution (Alpha Chem., 20 mL, 36 mmol) was added dropwise at 0 °C a solution of **2b** (1.0 g, 4.6 mmol) in anhyd ether (8 mL) over 20 min. After having been stirred at room temp for 6 h, the mixture was quenched by the addition of saturated NH_4Cl. Ether extract was washed with ammonia-water and brine, and the solvent was evaporated to give the product as a mixture with the starting material, from which **26** was obtained by silica gel chromatography (1:1 hexane-benzene). In other unavailing cases (see text), variable amount of the tertiary alcohol **24** and/or its dehydration product **25** formed in place of the 1,4-adduct **26**. **24**: ^1H NMR 0.74 (s, 3H), 0.74 (d, J = 5.8 Hz, 3H), 1.23 (s, 3H), 1.74 (br s, 3H), 4.84 (dd, J = 2.6,14.5 Hz, 1H), 5.02 (dd, J = 2.6,10.4 Hz, 1H), 5.54 (dd, J = 10.4,14.5 Hz, 1H). **25**: ^1H NMR 0.73 (d, J = 6 Hz, 3H), 0.78 (s, 3H), 1.74 (br s, 6H), 4.89 (dd, J = 2.4,16.2 Hz, 1H), 5.05 (dd, J = 2.4,10.4 Hz, 1H), 5.57 (dd, J = 10.4,16.2 Hz,

1H), 5.60 (m, 1H).

C. By dimethylcuprate addition to 2b at the presence of trimethylsilyl chloride.[50] A colorless clear solution of lithium dimethylcuprate was prepared from CuI (190 mg, 1 mmol) in THF (5 ml) and 1.0 M MeLi solution in ether (2 mL, 2 mmol) at -20 °C. To this solution pre-cooled to -78 °C was added successively trimethylsilyl chloride (freshly distilled from tri-n-butylamine, 545 mg, 5 mmol) and **2b** (109 mg, 0.5 mmol) in THF (0.5 ml). After removal of the cooling bath the mixture was allowed to react until the temperature become to 0 °C (ca. 1 h). Saturated NH_4Cl was added and the product was extracted with ether. Purification by preparative layer chromatography afforded **26** (21 mg, 17.5 %).

(±)-3,4,4aβ,5,6,7,8,8a-Octahydro-2-(bisdimethylamidophosphoryloxy)-1,5α,6α,8aβ-tetramethyl-5β-vinylnaphthalene (15). To a solution of the methylene ketone **13** (500 mg, 2.15 mmol) cooled at -78 °C was added dropwise 1M L-Selectride ® solution in THF (2.8 mL, 2.8 mmol) and , after removal of the cooling bath, the mixture was stirred for 1.5 h until the temperature raised to 0 °C. HMPA (0.7 mL) and bis(dimethylamino)- phosphorochloridate (2.4 mL, 16 mmol) were added successively and the mixture was allowed to react for 9 h, then quenched by the addition of aqueous $NaHCO_3$. The product was extracted with EtOAc and, after having been concentrated in vacuo, the extract was washed with $NaHCO_3$ solution and brine, and dried. Evaporation of the solvent yielded **15** as an oil (369 mg, 50.9%): IR(neat) 3080, 2800, 1240, 1075, 1000, 910 cm^{-1}; ^1H NMR 0.66(d, J = 6 Hz, 3H), 0.91(s, 3H), 1.03 (s, 3H), 1.63 (br s, 3H), 2.54(s, 6H), 2.66(s, 6H), 4.83 (dd, J = 2,17 Hz, 1H), 4.98 (dd, J = 2,11 Hz, 1H), 5.38(dd, J = 11,17 Hz, 1H). HRMS, calcd for $C_{20}H_{37}N_2O_2P$: 368.2590. Found: 368.2585.

(±)-2-(3,4,4aβ,5,6,7,8,8a-Octahydro-1,5α,6α,8aβ-tetramethylnaphthalen-5β-yl)ethanol (20). To a solution of the enol phosphate **15** (250 mg, 0.74 mmol) in anhyd THF (5 mL) was added 1M thexylborane solution in THF[67] (3.7 mL, 3.7 mmol) at 0 °C. The mixture was stirred for 7 h at ambient temp, followed by treatment with 30% H_2O_2 (10 mL) and 2M NaOH (40 mL) for 12 h. The product was extracted with EtOAc and the combined organic layers were washed successively with saturated $KHSO_3$, saturate $NaHCO_3$ and brine , and dried. Evaporation of the solvent gave crude product **17** (332 mg). In a three-necked flask equipped with a dry-ice condenser Li metal (280 mg, 40.3 mmol) was added to ethylamine (6 mL) containing tert-BuOH (0.5 ml). To this mixture stirred and kept at -20 °C was added dropwise a solution of the above product **17** in a mixture of THF (10 mL) and tert-BuOH (1 ml) in such way as the blue color of solution always persisted. After having been stirred at room temp for 10 min, the reaction mixture was quenched by the addition of solid NH_4Cl and the solvent was evaporated. The residue was diluted with water and the product was extracted with ether. The crude product obtained was purified by silica gel chromatography (4:1 hexane-ether) to furnish the alcohol **20** (98.6 mg, 56.4%): IR ($CHCl_3$) 3640, 3450, 1010 cm^{-1}; ^1H NMR 0.86 (s, 3H), 0.87(d, J = 7.5 Hz, 3H), 1.06 (s, 3H), 1.74 (d, J = 2 Hz, 3H), 3.75 (t, J = 7.5 Hz, 2H), 5.38 (br s, 1H); ^{13}C NMR 1.64(q), 17.0(q), 18.1(t), 19.8(q), 24.1(t), 28.8(t), 33.0(q), 37.0(s), 37.8(t), 38.5(d), 40.3(s), 40.9(t), 45.8(d), 58.9(t), 123.3(d), 139.8(s). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.27; H, 12.13. When the hydroboration-oxidation of **17** was conducted with diborane in THF, secondary alcohol **28** (17%) formed as a mixture of epimers in addition to **20** (41%) after Birch reduction and chromatographic separation (SiO_2). **28**: ^1H NMR 0.83, 0.98 (each d, J = 7 Hz, 3H in total), 1.01, 1.05 (each s, 3H in total), 1.09 (s, 3H), 1.25, 1.26 (each d, J = 6.4 Hz, 3H in total), 1.72, 1.73 (each br s, 3H in total), 3.96 (m, 1H), 5.40 (br s, 1H).

(±)-2-(3,4,4aβ,5,6,7,8,8a-Octahydro-1,5α,6α,8aβ-tetramethylnaphthalen-5β-yl)acetaldehyde (21). To a mixture of oxalyl chloride (0.01 mL, 0.11 mmol) and anhyd DMSO (0.02 mL, 0.28 mmol) in CH_2Cl_2 (0.5 mL) cooled at -78 °C was added dropwise a solution of the alcohol **20** (18.4 mg, 0.08 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 15 min, triethylamine (0.08 mL, 0.57 mmol) was added and the reaction mixture was allowed to warm gradually to -50 °C over 30 min. Water was added, the product was taken up in CH_2Cl_2 and the organic phase was washed with water and brine. The crude material obtained was purified by silica gel chromatography (95:5 hexane-ether) to give the aldehyde **21** (11 mg, 60%): IR($CHCl_3$) 2730, 1710, 1230, 1135, 1035 cm^{-1}; ^1H NMR 0.93(s, 3H), 0.95(d, J = 6.8 Hz, 3H), 1.06 (s, 3H), 1.72 (d, J = 1.6 Hz, 3H), 2.39 (dd, J = 3.5,15.1 Hz, 1H), 2.57 (dd, 3.5,15.1 Hz, 1H), 5.35 (br s, 1H), 9.90 (t, J = 3.5 Hz, 1H). HRMS, calcd for $C_{16}H_{26}O$: 234.1990. Found: 234.1996.

(±)-15,16-Epoxy-12-acetoxy-cis-cleroda-3,13(16),14-triene (23). To 3-lithiofuran solution prepared[68] from 3-bromofuran (0.03 mL, 0.33 mmol) in dry ether (1.0 mL) and n-butyllithium in hexane (1.45M, 0.2 mL, 0.29 mmol) was added a solution of the aldehyde **21** (11 mg, 0.047 mmol) in ether (1.0 mL) at -17 °C. Warming to -5 °C over 1 h, the reaction mixture was quenched by the addition of solid NH_4Cl. Ethe extrac-

tion followed by washing with brine, drying and evaporation of the solvent furnished a red-brown colored oil (17.1 mg), which was acetylated by treatment with acetic anhydride (0.5 mL) and anhyd pyridine (0.5 mL) at room temp for 12 h. Crude product obtained after usual workup was chromatographed on a column of silica gel (96:4 hexane-ether) to afford the acetate **23** (16 mg, 99%) as a diastereomeric mixture: ^{1}H NMR 0.72,0.87 (each d, J = 6 Hz, 3H in total), 0.82 (s, 3H), 1.02 (s, 3H), 1.67 (s, 3H), 1.98 (s, 3H), 5.23 (br s, 1H), 5.89 (m, 1H), 6.32 (br s, 1H), 7.28 (m, 2H).

(±)-15,16-Epoxy-cis-cleroda-3,13(16),14-triene (11). Lithium metal (25 mg, 3.6 mmol) was dissolved in liquid ammonia (6 mL) and to the resulting blue colored solution was added dropwise a solution of the acetate **23** (16 mg, 0.046 mmol) in THF (1.0 mL) at -78 °C. After having been stirred for 2 h, solid NH_4Cl was added and the ammonia was allowed to evaporate. Water was added to the residue and the product was isolated by ether extraction. The crude product was purified by silica gel chromatography (hexane), giving the target compound **11** (10.1 mg, 76%): IR(CCl_4) 1160, 1025, 870 cm^{-1}; ^{1}H NMR(CCl_4) 0.82 (d, J = 6.3 Hz, 3H), 0.82 (s, 3H), 1.05 (s, 3H), 1.71 (d, J = 1.6 Hz, 3H), 5.30 (br s, 1H), 6.20 (s, 1H), 7.16 (s, 1H), 7.28 (t, J = 1.6 Hz, 1H). HRMS, calcd for $C_{20}H_{30}O$: 286.2297. Found: 286.2302. The identity of this product with the natural product[35] have been confirmed by the comparison of IR and ^{1}H NMR spectra.

(±)-3,4,4aβ,5,6,7,8,8a-Octahydro-8aα-cyano-1α,5α,6α-trimethyl-5β-vinyl-2(1H)-naphthalenone (33). To a solution of the octalone **2b** (6.14 g, 28.2 mmol) in dry benzene (550 mL) was added dropwise diethylaluminum cyanide solution in toluene (55 mL of 2M solution, Alpha Chemicals, diluted with 150 mL of toluene, 110 mmol) over 1 h and the mixture was allowed to react at 28-35 °C for 2 h. It was poured on ice-cooled 5% sodium hydroxide and the product was taken up in ether. Ether layers were washed successively with 2M HCl, saturated $NaHCO_3$ and brine, and the solvent was evaporated. The residue was chromatographed on a column of silica gel (95:5 benzene-EtOAc) to give the cyanoketone **33** as crystals (5.72 g, 83%), needles (ether-hexane), mp 78.0-78.5: IR(CCl_4) 3110, 2235, 1725, 1635, 915 cm^{-1}; ^{1}H NMR 0.82 (d, J = 6.0 Hz, 3H), 1.04(s, 3H), 1.12 (d, J = 6.5 Hz, 3H), 4.98 (dd, J = 1.5,17 Hz, 1H), 5.13 (dd, J = 1.5,11 Hz, 1H), 5.46 (dd, J = 11,17 Hz, 1H); ^{13}C NMR 8.1(q), 9.8(q), 16.0(q), 25.1(t), 26.6(t), 35.7(t), 39.8(d), 40.9(t), 43.9(s), 45.1(s), 50.1(d), 53.8(d), 114.5(t), 120.4(s), 147.0(d), 206.9(s). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.18; H, 9.49; N, 5.69.

(±)-Decahydro-8aα-cyano-2-ethylenedioxy-1α,5α,6α-trimethyl-5β-vinylnaphthalene (34). A solution of the cynoketone **33** (3.12 g, 12.7 mmol) and ethyleneglycol (9.25 g, 149 mmol) in dry benzene containing catalytic amount of p-toluenesulfonic acid was refluxed for 7 h, while the water formed was removed by the use of Dean-Stark apparatus. The reaction mixture was diluted with ether and washed with saturated $NaHCO_3$ and brine, then dried with anhyd K_2CO_3. Evaporation of the solvent gave the ketal **34** (3.41 g, 93%) which crystallized as plates, mp 127-129.5 °C: IR(CCl_4) 3110, 2240, 1635, 1175, 1110, 1095, 1060, 915 cm^{-1}; ^{1}H NMR(CCl_4) 0.80 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.0 Hz, 3H), 1.05 (s, 3H), 3.95 (m, 4H), 4.93 (dd, J = 1.5,16 Hz, 1H), 5.08 (dd, J = 1.5,11 Hz, 1H), 5.37 (dd, J = 11,16 Hz, 1H). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.93; H, 9.50; N, 4.82.

(±)-2-(Decahydro-8aα-cyano-2-ethylenedioxy-1α,5α,6α-trimethylnaphthalen-5β-yl)-ethanol (35). To a solution of the crude ketal **34** (750 mg, 2.6 mmol) was added 0.8M diborane-THF solution (5 mL, 4 mmol) at 0 °C and the mixture was kept at room temp for 3 h. The reaction mixture was treated with 30% H_2O_2 and 2M NaOH (5 mL) under stirring for 3 h. The product was extracted with EtOAc and the extract solution was washed with saturated $NaHSO_3$ and brine, and dried. The residue left on evaporation of the solvent was chromatographed on a column of silica gel (4:1 hexane-ether). The secondary alcohol **43** (194 mg, 24%) and the primary alcohol **35** (450 mg, 56%) were eluted in succession. The compound **35** was obtained as white crystals, mp 194-199 °C: IR($CHCl_3$) 3610, 3450, 2235, 1175, 1095, 1180, 1150 cm^{-1}; ^{1}H NMR 0.91(d, J = 6 Hz, 3H), 0.99 (s, 3H), 1.07 (d, J = 7 Hz, 3H), 3.64 (t, J = 7 Hz, 2H), 3.99 (m, 4H). Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.26; H, 9.56; N, 4.44. **43** (mixture of diastereomers), crystals: ^{1}H NMR(400 MHz)[69] 0.86,† 0.99 (each d, J = 6.6 Hz, 3H in total), 1.05 (d, J = 6.8 Hz, 3H), 1.12, 1.14† (each s, 3H in total), 1.17,† 1.22 (each d, J = 6.8 and 6.6 respectively, 3H in total), 3.84-4.14 (m, 5H).

(±)-2-(Decahydro-8aα-cyano-2-ethylenedioxy-1α,5α,6α-trimethylnaphthalene-5β-yl)-acetaldehyde (36). Chromium trioxide (1.75 g, 17.5 mmol) was added to a mixture of pyridine (3 mL) and CH_2Cl_2 (30 mL) under stirring and cooling with an ice-salt bath.[70] A solution of the alcohol **35** (888 mg, 2.9 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 30 min. After the mixture was allowed to react for 3 h, the deep colored solution was separated from the black tarry deposit. The residu was washed

thoroughly with ether and then solvents were evaporated from the combined solution and washings. The residue was triturated with ether and the extract solution was filtered with the aid of Celite. The filtrate was washed successively with dil HCl, $NaHCO_3$ and brine. The crude product (823 mg) was purified by silica gel chromatography (5:1 CH_2Cl_2:AcOEt) to give aldehyde **36** as an oil: IR(CCl_4) 2715, 2215, 1720, 1175, 1105, 933 cm^{-1}; ^1H NMR 1.01 (d, J = 6 Hz, 3H), 1.06 (d, J = 6 Hz, 3H), 1.08 (s, 3H), 2.41 (d, J = 3 Hz, 2H), 3.99 (m, 4H), 9.71 (t, J = 3 Hz, 1H).

(±)-15,16-Epoxy-19-nitrilo-trans-cleroda-13(16),14-dien-3-one (38). A solution of the aldehyde **36** (345 mg, 1.18 mmol) in anhyd ether was added to 3-lithiofuran solution prepared from 3-bromofuran (0.21 mL, 2.34 mmol) in ether (6 mL) and 1.5M n-butyl lithium solution (1.6 mL, 2.4 mmol) at - 78 °C. After having been stirred for 1 h, the reaction mixture was quenched by the addition of NH_4Cl and worked up as before giving crude product which was dissolved in CH_2Cl_2 (3 mL) and treated with acetic anhydride (2 mL) and pyridine (2 mL) overnight at room temp. The acetate (417 mg) thus obtained was dissolved in THF (5 mL) and treated with lithium metal (170 mg, 0.48 mmol atom) in liquid ammonia (20 mL) at -78 °C for 15 min. Workup as usual afforded the 3-furyl ketal **37** as an oil (376 mg): ^1H NMR 0.88 (d, J = 6 Hz, 3H), 0.92 (d, J = 6 Hz, 3H), 0.99 (s, 3H), 3.97 (m, 4H), 6.18 (m, 1H), 7.17 (br s, 1H), 7.29 (s, 1H). The ketal **37** was hydrolyzed by treatment with 2M HCl (2.1 mL) in acetone (8.4 mL) at room temp for 1.5 h. The product was extracted with ether and the ether layers were washed with saturated $NaHCO_3$ and brine. The crude product was purified by silica gel chromatography (1:2 hexane-ether) to yield the 3-furyl ketone **38** as an oil: IR(CCl_4) 2235, 1725, 1165, 1065, 1028, 872 cm^{-1}; ^1H NMR(400 MHz) 0.93 (d, J = 6.1 Hz, 3H), 0.99 (s, 3H), 1.18 (d, J = 6.6 Hz, 3H), 6.27 (br s, 1H), 7.23 (br s, 1H), 7.37 (t, J = 1.7 Hz, 1H). HRMS, calcd for $C_{20}H_{27}NO_2$: 313.2042. Found 313.2047.

(±)-15,16-Epoxy-19-nitrilo-trans-cleroda-3,13(16),14-triene(40). To a 1M L-Selectride ® solution (0.9 mL, 0.9 mmol) diluted with THF (3 mL) was added a solution of the keto nitrile **38** (100 mg, 0.32 mmol) in THF (3 mL) at -78 °C and the mixture was stirred for 1 h. Having warmed to room temp the reaction mixture was treated with 30% H_2O_2 (2 mL) and 1M NaOH (8 mL). It was concentrated in vacuo and extracted with CH_2Cl_2 followed by washing ($NaHSO_3$ and brine) and drying. Evaporation of the solvent furnished the alcohol **39** as an oil: ^1H NMR(400 MHz) 0.88 (d, J = 6.4 Hz, 3H), 1.02 (s, 3H), 1.24 (d, J = 7.1 Hz, 3H), 3.82(m, $W_{1/2}$ = 8.3 Hz, 1H), 6.25 (br s, 1H), 7.20 (br s, 1H), 7.35 (t, J = 1.7 Hz, 1H). HRMS, calcd for $C_{20}H_{29}NO_2$: 315.2197. Found 315.2186. The above alcohol **39** was dissolved in pyridine (7 mL) and treated with phosphorus oxychloride (0.28 mL, 3 mmol) at room temp for 2 h. The reaction mixture was poured onto ice-water and the product was extracted with ether. The organic layers were washed with successively with 2M HCl, water, saturated $NaHCO_3$, and saturated brine. After drying the solvent was evaporated and the residue was purified by silica gel chromatography (5:1 hexane-ether) giving the dehydrated product **40** as an oil (66 mg, 70% from **38**): ^1H NMR 0.88 (d, J = 6 Hz, 3H), 0.99 (s, 3H), 1.77 (br s, 3H), 5.55 (m, 1H), 6.25 (br s, 1H), 7.20 (br s, 1H), 7.33 (t, J = 1.5 Hz, 1H).; ^{13}C NMR 15.9(q), 16.4(q), 17.8(t), 18.5(q), 20.6(t), 26.7(t), 28.1(t), 34.6(t), 36.0(d), 37.6(t), 39.0(s), 41.4(s), 46.4(d), 110.9(d), 123.4(s), 125.2(s), 126.4(d), 134.4 (s), 138.5(d), 142.9(d).

(±)-15,16-Epoxy-19-oxo-trans-cleroda-3,13(16),14-triene (41). To a solution of **40** (55 mg, 0.185 mmol) in toluene (3 mL) was added 1M diisobutylaluminum hydride solution in toluene (0.32 mL, 0.32 mmol) dropwise at 0 °C and the mixture was stirred at room temp for 2 h. Ice and EtOAc (30 mL) were added and the mixture was stirred vigorously for 1 h. After drying with anhyd $MgSO_4$, it was filtered with the aid of Celite. The residue obtained by the evaporation of the solvent was dissolved in THF (3 mL) and treated with a mixture of acetic acid (3 mL) and water (1.5 mL) at 100 °C for 1 h. Saturated $NaHCO_3$ was added cautiously and the product was isolated by the extraction with ether. The purification was performed by silica gel chromatography (20:1 hexane-ether to afford the aldehyde **41** as an oil (52 mg, 94%): IR(neat) 2725, 1702, 1160, 1025, 872 cm^{-1}; ^1H NMR 0.66 (s, 3H), 0.80(d, J = 6 Hz, 3H), 1.42 (d, J = 1.5 Hz, 3H), 5.73 (m, 1H), 6.20 (br s, 1H), 7.16 (br s, 1H), 7.30 (t, J = 1.5 Hz, 1H), 9.60 (d, J = 1.5 Hz, 1H). The H^1 NMR signals showed a good correspondance to those reported for the compound derived from maingayic acid.[60,61]

(±)-15,16-Epoxy-trans-cleroda-3,13(16),14-triene-19-oic acid, (±)-Maingayic acid (32). A solution of the aldehyde **41** (37 mg, 0.123 mmol) in tert-BuOH (0.3 mL) was mixed with NaH_2PO_4 solution (10 mg in 0.1 mL of water) and was treated with $NaClO_2$ (15 mg, 0.165 mmol) in the presence of tert-amylene (15 mg) at ambient temp for 20 h. The product was extracted with EtOAc and the organic layers were washed with water and brine, then dried. The residue left after evaporation of the solvent was separated by preparative layer chromatography (20:1 benzene-ethyl acetate) giving

the acid **32** (8 mg, 21%, 35% based on the converted material) with recovery of the starting aldehyde (40%). The acid product **32** showed following spectroscopic properties: IR(neat) 3200-2300, 1685, 1160, 875 cm^{-1}; ^1H NMR 0.71 (s, 3H), 0.83 (d, J = 6 Hz, 3H), 1.60 (br s, 3H), 5.52 (m, 1H), 6.21 (m, 1H), 7.16 (m, 1H), 7.29 (t, J = 1.5 Hz, 1H). Although the comparison of IR spectra did not provide clear indication for the purpose of the identification of the synthetic **32** with natural product, ^1H NMR spectra of both showed an excellent agreement. For the further confirmation the acid product **32** was converted to the methyl ester **44** by the treatment with an excess of ethereal diazomethane. After purification of the product by preparative layer chromatopgraphy (SiO_2, 5:1 hexane-ether) giving **(±)-methyl maingayate (44)**: IR(CCl_4) 1715, 1170, 1120, 1063, 1015, 1003, 870 cm^{-1}; ^1H NMR 0.58 (s, 3H), 0.83 (d, J = 6 Hz, 3H), 1.16 (s, 3H), 3.64 (s, 3H), 5.50 (m, 1H), 6.26 (m, 1H), 7.19 (m, 1H), 7.34 (t, J = 1.5 Hz, 1H). The IR spectrum was in conformity with the authentic one except the presece of additional absorption around 1220 cm^{-1} in the spectrum of μthe synthetic product which could not be removed after purification by HPLC (Porasil). The ^1H NMR spectra of the synthetic and natural methy ester **44** were superimposable.

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