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DIELS–ALDER REACTIONS OF SUBSTITUTED MALEIC ANHYDRIDES WITH 1-VINYLCOCLOHEXANE

STEREOSPECIFIC FORMATION OF A BICYCLIC INTERMEDIATE USEFUL FOR SYNTHESES OF CLERODANE DITERPENES[1,2]

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Abstract—The Diels–Alder reaction of 1-vinylcyclohexene with aconitic anhydride gives the adduct **5b** which has the reversed stereochemistry of that predicted by Alder's *endo* rule. On the other hand, reactions with chloromethylmaleic anhydride and citraconic anhydride afford *endo*-adducts **23** and **24**, respectively. Adduct **23** has the appropriate stereochemistry and functionality for the syntheses of clerodane and related diterpenes.

Clerodane diterpenes have a rearranged labdane skeleton and belong to a novel class of natural products[3] which recently have been found in nature in increasing numbers.[4,5] They also frequently show interesting physiological activities.[6] However, the totally synthetic approach to this type of diterpene had remained unexplored.[7] This report describes a stereospecific preparation by Diels–Alder reaction of a bicyclo[4.4.0]-decene intermediate, which has the stereochemistry at C-8, C-9 and C-10 pertinent to the construction of the clerodane skeleton 1.[10]

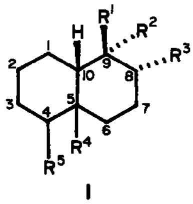

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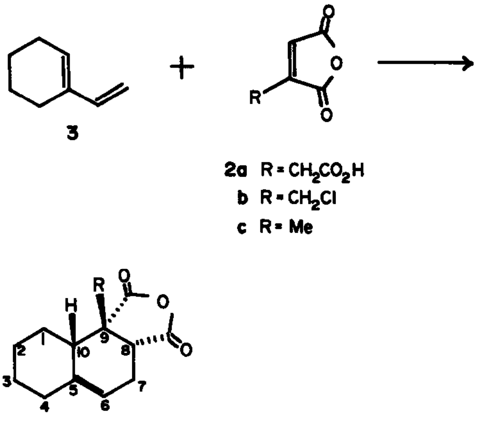
Fig. 1.

The two major classes of clerodane diterpenoids are distinguished by the ring junction—namely *trans*- and *cis*-clerodanes. Both types have a common characteristic array of asymmetric centers at C-8, C-9 and C-10, R^1 being six carbon side chains and R^2 and R^3 being one carbon substituents. R^5 also represents one-carbon substituents with a less significant stereochemical problem since C-4 is unsaturated in most clerodane molecules. Therefore, the key subject in the synthesis of clerodane diterpenes is the stereospecific construction of the three adjacent asymmetric centers at C-8, C-9 and C-10. Once this objective is achieved, the introduction of C-5 substituents (R^4) in an appropriate manner should lead to the syntheses of both *trans*- and *cis*-clerodane diterpenes.[4] Thus, we investigated the Diels–Alder reaction of substituted maleic anhydrides 2 with 1-vinylcyclohexene 3.[12] The products of this reaction could be presumed to have the configuration shown in 4, provided that stereochemical control operates in the direction expected from Alder's *endo* rule.[13–16]



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2a $R = CH_2CO_2H$
b $R = CH_2Cl$
c $R = Me$

4

Scheme 1.

Aconitic anhydride **2a** was selected as a dienophile. The reaction of **2a** with **3** at 95–105° for 23 h and subsequent methylation with diazomethane afforded the methyl ester **5**, m.p. 172–173°, of an adduct in 26% yield. Chromatographic investigation indicated that the rest of the products consisted of polymeric materials and no compounds existed which were positionally or stereochemically isomeric with **5**. Although the available data (elemental analysis, IR and NMR) were consistent with the formulation as an adduct, they were not sufficient to differentiate between the four possible structures **5a–5d**. Performic acid oxidation of **5** followed by treatment with 2 N NaOH solution and methylation with diazomethane afforded a hydroxy-γ-lactone **6** (ν_{max} 3440, 1770 and 1730 cm^{-1}), which on acetylation with acetic anhydride and pyride gave an acetate **7** (ν_{max} 1780, 1735 and 1720 cm^{-1}). The IR and NMR spectra of **7** indicated the presence of a secondary carbomethoxy group and a γ-lactone ring. This fact suggests that **6** was produced by lactonization of the tertiary carboxyl group of the anhydride grouping in **5** with the tertiary hydroxyl group formed on per-acid oxidation. In the NMR spectrum of

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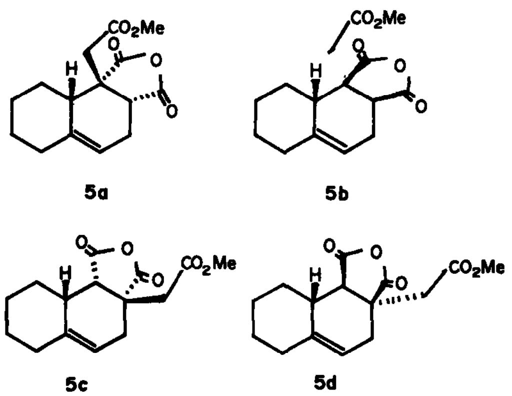
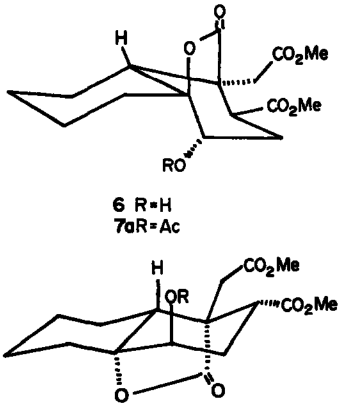


5a 5b 5c 5d

Fig. 2.

7, the signal due to the protons on the carbon atoms bearing the secondary carbomethoxy and acetoxy groups were both double doublets at δ 3.29 (J = 6 and 12 Hz) and 4.86 ppm (J = 2 and 4 Hz), respectively. These facts signify that a methylene group is contiguous to the tertiary carbon atom (C-8) bearing a carbomethoxy group, and only **7a** and **7b** are tenable for the expression of **7**. The magnitude of the coupling constants denotes that the conformations of the carbomethoxy and the acetoxy groups are equatorial and axial, respectively, which is consistent with both formulations **7a** and **7b**. Thus either formula **5a** or **5b** predicted from existing regioselectivity rules for the Diels–Alder reaction,[17,18] was acceptable as the structure of the adduct, but discrimination between them was not possible at this stage.

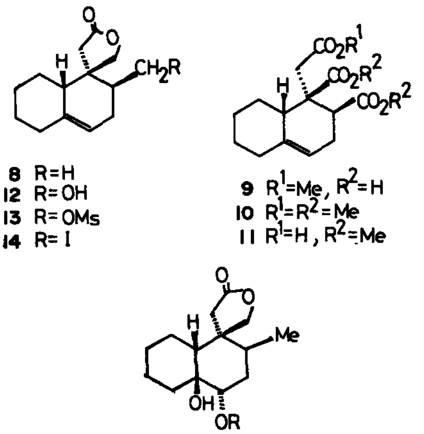


6 R=H
7aR=Ac

7b R=Ac

Fig. 3.

In order to define the stereochemistry of adduct **5** and test the possibility of further structural transformation necessary for the syntheses of clerodane diterpenes, attention was directed to the conversion of **5** into γ-lactone **8**. For this, selective reduction of two of the three carboxyl functions in **5** was done. First, selective reduction of the carboxyl groups in the monoester dicarboxylic acid **9**, obtained from **5** by hydrolysis, was attempted by means of diborane treatment[19] or sodium borohydride reduction of the resultant formic anhydride,[20] but neither gave satisfactory results. Next, selective reduction of the ester group vs the carboxyl group was tried. The substrate dimethyl ester monocarboxylic acid **11** was obtained through partial hydrolysis of the trimethyl ester **10**, which in turn was obtained by methylation of **9**. On treatment of **11** with sodium trimethoxyborohydride,[21,22] the desired selective reduction occurred smoothly and after subsequent acid treatment, the hydroxy-γ-lactone **12** (ν_{max} 3450 and 1770 cm^{-1}) was obtained in 75% yield. Reductive removal of the hydroxyl group was performed by a sequence of reactions: mesylation, substitution with iodide (NaI–acetone) and reduction (Zn–AcOH). In accordance with the gross structure **8**, the product, m.p. 86–87°, exhibited an IR peak at 1765 cm^{-1} due to the γ-lactone ring and NMR signals at δ 0.98 (3H, d, J = 6 Hz, $-\overset{|}{C}HCH_3$),[a] 2.24, 2.64 (2 H, AB quartet, J = 10 Hz, $-CH_2OCO-$) and 5.34 ppm (1 H, br s, $-\overset{|}{C}{=}CHCH_2-$). The stereochemistry of **8** was assigned in the following way. **8** was oxidized with performic acid to obtain a secondary formate **15** [ν_{max} 3440, 1760 and 1720 cm^{-1}; δ 4.72 (1 H, br, s, $-\overset{|}{C}\underline{H}OCHO$) and 8.14 (1 H, s, $-\overset{|}{C}HOC\underline{H}O$)], which was hydrolyzed to a *trans*-diol **16**. If the per-acid attack occurred at the less hindered convex side of **8** and the intermediary epoxide **17**[b] underwent *trans*-diaxial opening (Scheme 2), the tertiary hydroxyl and the secondary formyl groups in the product **15** must have the conformation depicted in **15a**. In accordance with this deduction, the NMR spectrum of **15** exhibited the signal of the proton attached to the carbon atom bearing the formyloxy group as a narrow multiplet ($W_{1/2}$ = 5 Hz) and the AB quartet due to the hydroxymethylene protons of the γ-lactone ring at considerably lower field ($\Delta\delta$ = 0.20 ppm) compared to that of **8**, whereas the chemical shift of the AB quartet due to the carbonyl methylene protons remained unchanged from **8** to **15**. The latter fact indicated that the tertiary hydroxyl group introduced in **15** was axial and exerted a prominent deshielding effect on the hydroxymethylene group,[24] and at the same time



8 R=H
12 R=OH
13 R=OMs
14 R=I

9 R^1=Me, R^2=H
10 R^1=R^2=Me
11 R^1=H, R^2=Me

15 R=CHO
16 R=H

Fig. 4.

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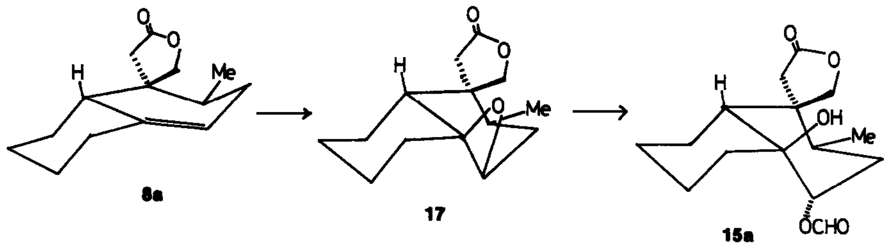
[a] This signal appeared as a somewhat "filled in doublet" type by virtual coupling.[23] The same tendencies were observed in **15** and **18**, but not in **19**.

[b] The corresponding steroidal conformation might be taken into account. However such a conformation would be decidely less stable than nonsteroidal **17** owing to the severe steric interaction between the carbonyl methylene group of the γ-lactone ring and the C-2 methylene groups and C-4. See also the discussion below on the conformation of **25** and **26**.



Scheme 2.

defined the configuration of this lactone ring as shown in **15**. The *cis*-diol **18** obtained by osmium tetroxide oxidation, where the approach of the bulky reagent from the less hindered convex side was reasonably assumed, likewise exhibited NMR signals due to the hydroxymethylene protons at a field lower than that of **8** by $\Delta\delta = 0.18$ ppm. Both the *trans*-diol **16** and the *cis*-diol **18** afforded the same ketol **19** on oxidation with Jones' reagent. This configuration of **8** was supported by its synthesis by another route (Scheme 3).

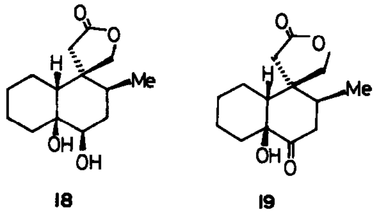
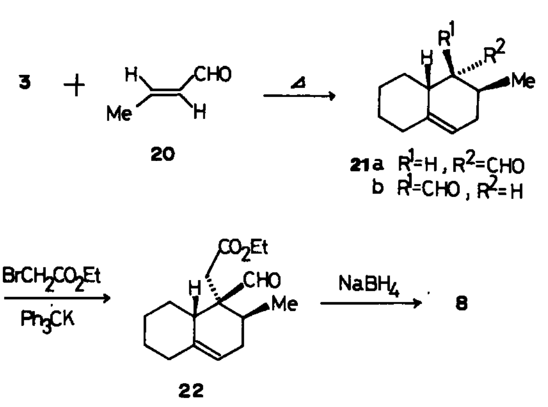


Fig. 5.

Dien reaction of 1-vinyl cyclohexene **3** with *trans*-croton aldehyde **20** at 130–140° yielded an adduct **21**,[c] which was alkylated with ethyl bromoacetate and triphenylmethyl potassium to give **22**. Subsequent reduction of **22** with sodium borohydride followed by acid treatment furnished a product identical with **8** albeit in low yield. This result can be explained by assuming



Scheme 3.

that the Diels–Alder adduct **21** has the configuration expected from the *endo* rule[14–16] as in **21** (irrespective of the configuration at C-9) and its alkylation has occurred from the α- rather than the β-side due to hindrance by the quasi-axial methyl group at C-2. Thus we concluded that **8** has the configuration shown above and the Diels–Alder adduct must be depicted by **5b**. This meant that **5** has the reversed stereochemistry of that predicted from Alder's *endo* rule and is unsuitable as the intermediate for the syntheses of clerodane diterpenes.

In order to understand this unexpected result, Diels–Alder reactions of 1-vinylcyclohexene with differently substituted maleic anhydrides were examined. The reactions of 1-vinylcyclohexene with chloromaleic anhydride **2b** and citraconic anhydride **2c** proceed at lower temperature (65°) than in the case of aconitic anhydride **2a** to afford the adducts **23**, m.p. 112–113° (71.5% yield), and **24**, m.p. 98–99° (50% yield) respectively. NMR spectra and other data of both products substantiated the

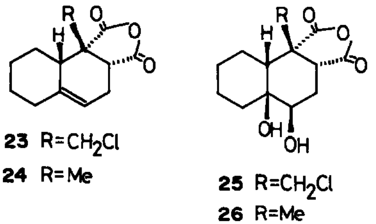
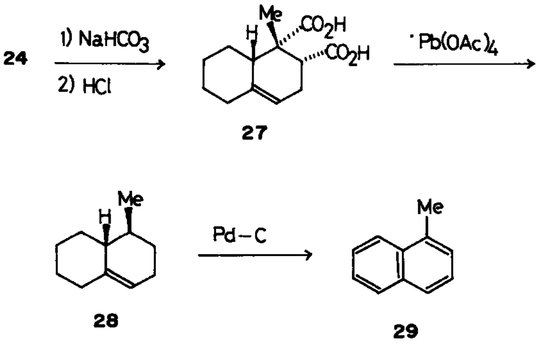


Fig. 6.

gross structures expected as Diels–Alder adducts. Since the reduction of **23** with zinc dust furnished **24**, they were products of common orientation and stereochemistry. The normal orientation in the formations of **23** and **24** were confirmed by the following conversion, shown here for **24**. Namely, the dicarboxylic acid **27** obtained by the hydrolysis of **24** was bisdecarboxylated with lead tetraacetate to give the diene **28**. Dehydrogenation of **28** in the presence of 30% palladium-charcoal at 300° afforded 1-methylnaphthalene **29**. Stereochemical assignment of **23** and **24** was performed by transforming them into the corresponding diols **25** and **26**. Two possible conformations of both **25** and **26** were considered: "nonsteroidal" **31** and "steroidal" **32**. Inspection of the models suggested **31** would be preferred to **32** since in the latter, a severe steric interaction could be predicted between the oxygen atom of the C-9 carbonyl group and



Scheme 4.

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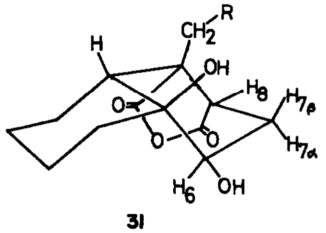
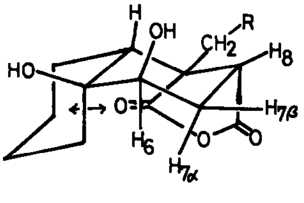
[c] **21** was obtained as a mixture of *trans* and *cis* epimers **21a** and **21b** in a ratio of approximately 3 : 1. On treatment with basic alumina this ratio reversed to 1 : 8. See the Experimental section.

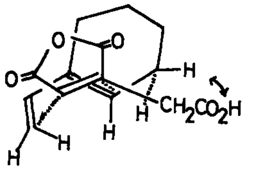


31

Fig. 7.



32



30

Fig. 8.

the axial hydrogen atom at C-2. This presumption agreed with the NMR analyses of **25** and **26**. The four protons on the contiguous carbon atoms, C-6, C-7 and C-8 in both **25** and **26** constitute an ABMX spin system and allow first-order analysis. The coupling constants listed in Table 1 are interpretable only in terms of conformation **31**. The somewhat larger values of $J_{H\text{-}6,H\text{-}7\alpha}$ and $J_{H\text{-}7\beta,H\text{-}8}$ expected from the dihedral angles may reasonably be ascribed to the ring distortion caused mainly by the attachment of the 5-membered anhydride grouping. On the basis of the established ring conformations of **25** and **26**, we can discuss the configuration of the substituents in them. In the NMR spectra, the AB quartet due to the chloromethyl group in the case of **25** and the methyl singlet in the case of **26** shift to lower field by 0.78 and 0.33 ppm respectively, compared with those of **23** and **24** respectively. Thus, we concluded that **23** and **24** have the orientation and configuration of substituents predicted by the general rules existing for the Diels–Alder reaction. Eventually **23** has the desired stereochemistry at C-1, C-2 and C-10 with appropriate functionalities for the syntheses of clerodane and related diterpenes, and could be a useful intermediate for obtaining them.[10]

It is remarkable from the view of stereoselectivity of the Diels–Alder reaction that contrasting results were obtained from the reactions of 1-vinylcyclohexene **3** with the substituted maleic anhydrides studied. The reaction of **3** with aconitic anhydride **2a** produced the *exo*-adduct **5b** while those with chloromethylmaleic anhydride **2b** and citraconic anhydride **2c** led to the formation of the *endo*-adducts **23** and **24**. *Endo* stereoselectivity in the Diels–Alder reaction is currently being appraised both theoretically and experimentally.[25–33] Of the various factors introduced to explain it,[27,29,30,34–39] the steric one[27,32,33] seems to be responsible for the discrepancy in the present case. Whereas the reactions of **2b** and **2c** with **3** proceed normally to yield *endo* products as expected from the secondary orbital interactions, in the reaction of **2a** with **3**, the *endo* transition state like **30** would become energetically unfavorable due to the enhanced steric repulsioon between the carboxyl group in **2a** and the C-3 methylene group in **3**. This would lead to the addition of **2a** to **3** from the *exo* direction, despite the disadvantage with respect to orbital interactions.[40–42] The stereoselectivity in the Diels–Alder reactions of 1-vinylcyclohexene with substituted maleic anhydrides seems to provide an interesting problem form the viewpoint of secondary orbital effects vs steric effects, and may deserve further study.

EXPERIMENTAL

All m.p. are uncorrected. Merck silica gel was used for column chromatography. IR spectra were recorded as films (liquid) or Nujol mulls (solid) on a JASCO IRA-1 spectrometer. NMR spectra were taken, unless otherwise stated, in $CDCl_3$ on a JEOL PS-100 or, in some cases a JEOL HL-60 spectrometer. Signals are recorded as δ values (ppm) using TMS as an internal standard; multiplicity abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Microanalyses were carried out at the Microanalytical Laboratory, Faculty of Science, Osaka City University.

Diels–Alder reaction of 1*-vinylcyclohexene* **3** *with aconitic anhydride* **2a**. A solution of 1-vinylcyclohexene (15 g, 0.14 mole) and aconitic anhydride (22.5 g, 0.144 mole) in dioxane (70 ml, freshly distilled over Na) was charged in a glass pressure bottle with a small amount of hydroquinone and the mixture was heated at 95–105° for 23 h. The resulting tarry material was separated by decantation and triturated with anhyd. THF. To the combined solution was added ethereal diazomethane (dried with KOH) and the mixture was allowed to react for 3 h. Evaporation of the solvents left a viscous brown product (32 g) which was chromatographed on a column of SiO_2-gel (300 g). The $CHCl_3$ eluate was

Table 1. Coupling constants of proton signals in the ABMX systems appearing in NMR spectra of **31** and **32**

	Dihedral angle		Observed coupling constants (Hz)	
	31	**32**	**31**	**32**
$J_{H\text{-}6,H\text{-}7\alpha}$	60°	60°	5.5	6
$J_{H\text{-}6,H\text{-}7\beta}$	180°	60°	11	11
$J_{H\text{-}7\alpha,H\text{-}8}$	60°	180°	2	2
$J_{H\text{-}7\beta,H\text{-}8}$	60°	60°	7.5	7
$J_{H\text{-}7\alpha,H\text{-}7\beta}$	--	--	14	14

recrystallized from anhyd C_6H_6 giving **5b** as crystals (9.7 g, 26% yield). IR: 1835, 1770, 1725, 1230, 1020, 935, 915, 830 cm^{-1}; NMR: 2.75, 2.91 (AB q, J = 19 Hz, $-C\underline{H}_2CO_2Me$), 3.70 (3 H, s, $-CH_2CO_2\underline{Me}$), 5.25 (1 H, br s, $-\overset{|}{C}=C\underline{H}CH_2-$). (Found: C, 64.86; H, 6.50. $C_{15}H_{18}O_5$ requires: C, 64.73; H, 6.52%).

Oxidation of **5b** *with performic acid. Derivation of* **7a**. The adduct methyl ester **5b** (300 mg, 1.08 mmoles) was dissolved in formic acid (12 ml) then 30% H_2O_2 (0.3 ml) was added. After the mixture had been kept at 40° for 5 h, most of the formic acid was carefully distilled *in vacuo* and the residue was hydrolyzed by treatment with 2 N NaOH (10 ml) at 75–80° for 30 min. The reaction mixture was acidified with 1 N H_2SO_4 and heated shortly in a water bath. The product was extracted with ether and the extract was washed with sat NaCl aq (×3), dried over Na_2SO_4, and freed of the solvent. The obtained semi-solid (190 mg) was dissolved in MeOH and methylated with ethereal diazomethane to afford 210 mg of **6**. IR: 3440, 1770, 1730, 1195, 1165, 1075, 1050, 945 cm^{-1}. NMR: 2.51, 2.67 (AB q, J = 19 Hz, $-C\underline{H}_2CO_2Me$), 3.42 (1H, dd, J = 6, 12 Hz, $-\overset{|}{C}\underline{H}CO_2Me$), 3.64, 3.67 (each 3H, s, $-CO_2Me$), 3.80 (1 H, dd, J = 2, 4 Hz, $-CH_2\overset{|}{C}\underline{H}OH$). The above dimethyl ester **6** (175 mg) was acetylated with Ac_2O (2 ml) and pyridine (2 ml) at room temperature overnight and the product was recrystallized from EtOH to yield **7a** as crystals, m.p. 120–121°. IR: 1780, 1735 (sh), 1720, 1220, 1240, 1205, 1195, 1045 cm^{-1}. NMR: 2.10 (3 H, s, $-OCOMe$), 2.52, 2.64 (AB q, J = 18 Hz, $-CH_2CO_2Me$), 3.29 (1 H, dd, J = 6, 12 Hz, $-CH_2\overset{|}{C}\underline{H}CO_2Me$), 3.64, 3.68 (each 3 H, s, $-CO_2Me$), 4.86 (1 H, dd, J = 2, 4 Hz, $-\overset{|}{C}HOAc$). (Found: C, 58.57; H, 6.60. $C_{18}H_{24}O_8$ requires: C, 58.69; H, 6.57%).

Conversion of **5b** *into the dimethyl ester monocarboxylic acid* **11**. A suspension of **5b** (17.8 g) in sat $NaHCO_3$ aq (450 ml) was warmed at 90–100° for 4 h until all of the meaterial went in solution. After cooling, the solution was acidified by 1 N H_2SO_4 and the resulting precipitate was filtered giving the monomethyl ester dicarboxylic acid **9** (17.23 g) as a white solid. IR: 2600 (br), 1725, 1700 cm^{-1} (br). NMR (C_5D_5N): 3.44, 3.56 (AB q, J = 16 Hz, $-C\underline{H}_2CO_2Me$), 3.63 (3 H, s, $-CO_2Me$), 3.88 (1 H, dd, J = 6, 9 Hz, $-CH_2\overset{|}{C}\underline{H}CO_2H$), 5.50 (1 H, m, $-\overset{|}{C}=C\underline{H}CH_2-$). This acid dissolved in THF was methylated with excess ethereal diazomethane to produce the trimethyl ester **10** (17.23 g) as an oil. IR: 1730 (sh), 1720, 1165 cm^{-1}. NMR: 2.87 (2 H, s, $-C\underline{H}_2CO_2Me$), 3.05 (1 H, dd, J = 6, 8 Hz, $-CH_2\overset{|}{C}\underline{H}CO_2Me$), 3.72, 3.74, 3.77 (each 3 H, s, $-CO_2Me$), 5.42 (1 H, br s, $-\overset{|}{C}=C\underline{H}CH_2-$). This trimethyl ester **10** was dissolved in a mixture of MeOH (680 ml) and H_2O (650 ml), then treated with NaOH (2.76 g, 69 mmoles) under refluxing for 30 min. After cooling, the reaction mixture was neutralized with 1 N H_2SO_4 and MeOH was evaporated *in vacuo*. The residual solution was acidified and extracted with ether. The organic layers were washed with sat NaCl aq, dried over Na_2SO_4 and evaporated. The partially hydrolyzed ester **11** was obtained as a white powder (15.1 g, 76.1% yield from **5b**). IR: 2700–2500 (br), 1730, 1700, 1230, 1210, 1170 cm^{-1}. NMR (C_5D_5N): 3.47, 3.71 (AB q, J = 16 Hz, $-C\underline{H}_2CO_2H$), 3.77 (6 H, s, 2 × $-CO_2Me$), 4.02 (1 H, dd, J = 6, 10 Hz, $-CH_2\overset{|}{C}\underline{H}CO_2Me$), 5.58 (1 H, m, $-\overset{|}{C}=C\underline{H}CH_2-$).

Hydroxylactone **12**. *Selective reduction of the monocarboxylic acid dimethyl ester* **11**. A solution of **11** (15 g, 0.05 mole) in THF (70 ml) was added dropwise during 25 min to a stirred solution of $NaBH(OMe)_3$, prepared by the reaction of $B(OMe)_3$ (160 g, 1.54 mole) with NaH (50% oil dispersion, 86 g, washed with *n*-pentane) in THF (1.5 l).[43] The mixture was heated under refluxing for 3.5 h then stirred overnight at room temp. After concentration *in vacuo* (40°), the reaction mixture was poured onto ice water, acidified with 2 N H_2SO_4 and warmed for a while in a water bath. NaCl was added to the cooled mixture and the organic layer was separated. The aq phase was extracted with ether (×3). The combined organic extracts were washed with sat NaCl aq, dried over Na_2SO_4 and the solvent was evaporated. The product was purified by chromatography on a column of SiO_2–gel (300 g). Elution with $CHCl_3$ containing 2% MeOH afforded **12** as a colorless viscous oil (10.9 g, 96.3% yield). IR: 3380, 1755, 1180, 1030, 1000, 815 cm^{-1}. NMR: 2.26, 2.86 (AB q, J = 18 Hz, $-CH_2CO_2-$), 3.39 (1 H, dd, J = 5, 10.5 Hz, $-\overset{|}{C}HC\underline{H}_2OH$), 3.56 (1 H, dd J = 6, 10.5 Hz, $-\overset{|}{C}HC\underline{H}_2OH$), 4.14, 4.32 (2 H, AB q, J = 10 Hz, $-CH_2O_2C-$), 5.32 (1 H, br s, $-\overset{|}{C}=C\underline{H}CH_2-$).

Conversion of **12** *into lactone* **8**. To a solution of the hydroxy lactone **12** (10.9 g, 46.2 mmoles) in pyridine (50 ml) was added mesyl chloride (25 ml) and the mixture allowed to stand overnight at room temp. The dark red reaction mixture was worked up in the usual manner and the crude product purified by chromatography on a column of SiO_2–gel (300 g). Elution with $CHCl_3$ containing 1.5% MeOH furnished a mesyl ester **13** as crystals, m.p. 113–115° (10.58 g, 73% yield). IR: 1775, 1335, 1170, 1035, 945, 820 cm^{-1}. NMR: 2.38, 2.58 (AB q, J = 10 Hz, $-CH_2CO_2-$), 3.01 (3 H, s, $MeSO_3-$), 4.07, 4.40 (AB q, J = 10 Hz, $-CO_2CH_2-$), 4.19 (2 H, d, J = 7 Hz, $-\overset{|}{C}HC\underline{H}_2OMs$), 5.35 (1 H, m, $-\overset{|}{C}=CHCH_2-$) (Found: C, 57.04; H, 7.10. $C_{15}H_{27}OS_5$ requires C, 57.30; H, 7.07%). The above methyl ester (10.5 g, 33.44 mmoles) was refluxed with NaI (50 g, dried *in vacuo* at 100°) in anhyd acetone (700 ml) for 23.5 h. Most of the solvent was removed then H_2O was added. Extraction with $CHCl_3$ afforded the crystalline product (11.44 g, 99.2% yield) which was recrystallized from benzene to yield the pure iodide **14**, m.p. 129–130°. IR: 1775, 1175, 1025, 955, 860, 820 cm^{-1}. NMR: 2.35, 2.59 (AB q, J = 18 Hz, $-CH_2CO_2-$), 3.11 (1 H, t, J = 9 Hz, $-\overset{|}{C}HC\underline{H}_2I$), 3.35 (1 H, dd, J = 3, 9 Hz, $-\overset{|}{C}HC\underline{H}_2I$), 4.02, 4.32 (AB q, J = 10 Hz, $-CH_2OCO_2-$), 5.32 (1 H, br, s, $-\overset{|}{C}=C\underline{H}CH_2-$). (Found: C, 48.70; H, 5.61. $C_{14}H_{19}O_2I$ requires C, 48.56; H, 5.54%). This iodide **14** (10.8 g, 31.3 mmoles) dissolved in AcOH (250 ml) was treated with zinc dust (50 g) overnight at room temp. under stirring. Excess zinc was removed by filtration and washed thoroughly with AcOH. The filtrate and the washing were concentrated. $CHCl_3$ and H_2O were added to the residue and the aq layer was extracted twice with $CHCl_3$. The combined $CHCl_3$ layers were washed successively with sat $NaHCO_3$ aq, sat brine and dried over Na_2SO_4. Evaporation of the solvent gave a crystalline product (6.5 g, 94.3% yield) which was recrystallized from *n*-hexane to furnish a pure specimen of the lactone **8**, m.p. 86–87°. IR: 1765, 1180, 1020, 815 cm^{-1}. NMR: 0.98 (3 H, d, J = 6 Hz, with additional splitting by virtual coupling, $\underline{Me}\overset{|}{C}HCH_2-$), 2.24, 2.64 (2 H, AB q, J = 18 Hz, $-CH_2CO_2-$), 4.02, 4.18 (2 H, AB q, J = 10 Hz, $-CH_2OCO_2-$), 5.34 (1 H, br s, $-\overset{|}{C}=C\underline{H}CH_2-$). (Found: C, 75.92; H, 9.08. $C_{14}H_{20}O_2$ requires: C, 76.32; H, 9.15%).

Performic oxidation of lactone **8**. H_2O_2 (30%) was added to the ice-cooled solution of lactone **8** (110 mg, 0.5 mmole) in formic acid (3 ml) and the mixture was allowed to react at 40° for 4 h. Next, the reaction mixture was concentrated, H_2O (5 ml) was added and this mixture was warmed at 80° for 2 h. The product was isolated by ether extraction giving the hydroxyformate **15** (100 mg) as a crystalline solid, m.p. 185°. IR: 3440, 1760, 1720 cm^{-1}. NMR: 0.93 (3 H, d, J = 6 Hz, virtually coupled, $\underline{Me}\overset{|}{C}HCH_2-$), 2.17, 2.67 (2 H, AB q, J = 18 Hz, $-CH_2CO_2-$), 4.17, 4.43 (2 H, AB q, J = 11 Hz, $-CO_2CH_2-$), 4.72 (1 H, m, $W_{1/2}$ = 5 Hz, $-C\underline{H}(OCHO)CH_2-$), 8.14 (1 H, s, $-OCHO$). The hydroxyformate **15** (80 mg, 0.82 mmole) was hydrolyzed by heating with 2 N NaOH (3 ml) at 75–80°. A usual work-up yielded the *trans*-diol **16** as a colorless glass (75 mg). IR: 3420, 1760, 1190, 1015 cm^{-1}. This diol **16** (80 mg) was dissolved in dry acetone (5 ml) and oxidized with Jones' reagent (0.13 ml)[44] at 0° for 1 h. Work-up afforded the ketol **19** as a colorless glass (80 mg). IR: 3440, 1760, 1710, 1195, 1010, 995 cm^{-1}. NMR: 1.05 (3 H, d, J = 7 Hz, $-\overset{|}{\mathrm{C}}\mathrm{H\underline{Me}}$), 2.12, 2.72 (2 H, AB q, J = 18 Hz, $-\mathrm{CH_2CO_2}-$), 2.07 (1 H, dd, J = 3, 14 Hz, $-\mathrm{COC\underline{H}_2}\overset{|}{\mathrm{C}}\mathrm{H}-$), 3.01 (1 H, t, J = 14 Hz, $-\mathrm{COC\underline{H}_2}\overset{|}{\mathrm{C}}\mathrm{H}-$), 4.37, 4.59 (2 H, AB q, J = 11 Hz, $-\mathrm{CO_2CH_2}-$).

OsO_4 Oxidation of lactone **8**. To a solution of lactone **8** (110 mg, 0.5 mmole) in ether (2 ml) was added a solution of OsO_4 (140 mg, 0.55 mmole) in ether (5 ml) containing pyridine (0.1 ml, 1.265 mmole). After the mixture had been stirred overnight at ambient temperature, it was saturated with H_2S gas. The black precipitate which formed was removed by filtration then washed with THF. Evaporation of the solvent from the combined filtrate and washings afforded a semi-solid (145 mg) which was purified by SiO_2–gel chromatography to yield the *cis*-diol **18** (110 mg, 87% yield), m.p. 128–128.5°. IR: 3500, 1760, 1190, 1015, 990 cm^{-1}. NMR: 0.97 (3 H, m, virtually coupled, $\mathrm{\underline{Me}}\overset{|}{\mathrm{C}}\mathrm{HCH_2}-$), 2.08, 2.68 (2 H, AB q, J = 18 Hz, $-\mathrm{CH_2CO_2}-$), 3.33 (1 H, m, $W_{1/2}$ = 17 Hz, $-\overset{|}{\mathrm{C}}\mathrm{\underline{H}OHCH_2}-$), 4.12, 4.44 (2 H, AB q, J = 11 Hz, $-\mathrm{CO_2CH_2}-$). (Found: C, 66.05; H, 8.75. $C_{14}H_{22}O_4$ requires: C, 66.01; H, 8.72%). When this diol **18** (110 mg) was oxidized with Jones' reagent in the same way as in the case of the *trans*-diol **16**, the same ketol **19** (50 mg) was obtained after chromatographic purification and identified by comparison of IR spectra.

Diels–Alder reaction of 1-*vinylcylohexene* **3** *with* trans-*crotonaldehyde*. A mixture of 1-vinylcyclohexene (5.4 g, 50 mmoles), croton aldehyde (3.5 g, 50 mmoles) and a small amount of hydroquinone was heated in a sealed tube at 130–140° for 24 h. The reaction mixture was distilled *in vacuo* to give 3.38 g of adduct **21** as a mixture of epimers **21a** and **21b** (*ca.* 3:1 ratio, GLC analysis). Treatment of this mixture with basic Al_2O_3 in benzene for 15 h reversed the ratio of the epimers to *ca.* 1:8. Pure **21b** was available through preparative GLC (20% DEGS colum). IR; 2660, 1720, 1050, 815 cm^{-1}. NMR: 0.88 (3 H, d, J = 7 Hz, $\mathrm{\underline{Me}}\overset{|}{\mathrm{C}}\mathrm{H}-$), 5.22 (1 H, m, $-\overset{|}{\mathrm{C}}\mathrm{=C\underline{H}CH_2}-$), 9.63 (1 H, d, J = 2 Hz, $-\overset{|}{\mathrm{C}}\mathrm{HC\underline{H}O}$).

Conversion of Diels–Alder adduct **21** *into* **8**. To a solution of triphenylmethyl potassium prepared from triphenylmethane (5.54 g, 24.7 mmoles), potassium (930 mg, 23.75 mg atoms) and 1,2-dimethoxyethane (30 ml) was added adduct **21** (3.38 g, 19 mmoles) until the red color of the solution disappeared. The reaction mixture was stirred at room temp for 15 min and at 50–60° for 45 min. Subsequently, ethyl bromoacetate (7.9 g, 47.5 mmoles) was added dropwise at this temperature. The mixture was heated under refluxing for 20 h. The inorganic precipitate was removed by filtration and washed thoroughly with THF. The solvent was evaporated, H_2O was added and the product was extracted with ether. The ether layers were washed with sat NaCl aq, dried over Na_2SO_4 and the solvent was evaporated. The resulting pale yellow oil (15.52 g), without further purification, was dissolved in ethanol (70 ml) and treated with $NaBH_4$ (1.5 g) at room temp. for 17 h. The solution was concentrated, then H_2O was added and the mixture was acidified with 1 N H_2SO_4. The mixture was heated on a water bath for a while, then the product was isolated by ether extraction giving an oil (13.78 g), which was chromatographed on a column of SiO_2–gel (250 g). $CHCl_3$ elution yielded lactone **8** (195 mg), which was identified by comparison of IR and NMR.

Chloromethylmaleic anhydride **2b**. This compound was prepared essentially by the method of Eschenmoser.[45] Chlorination of itaconic anhydride afforded 88% yield of 3-chloro-3-chloromethyl-butan-1,4-dioic anhydride, b.p. 125–126°/15 mmHg. NMR: 3.31, 3.73 (2 H, AB q, J = 20 Hz, $-\mathrm{CH_2CO_2}-$), 3.91, 4.21 (2 H, AB q, J = 12 Hz, $-\mathrm{CH_2Cl}$). The dichloro compound was pyrolyzed at 210° for 3 h giving 74% yield of chloromethylmaleic anhydride, b.p. 74.5–75.5°/0.8 mm Hg. NMR: 4.40 (2 H, d, J = 2 Hz, $\mathrm{ClC\underline{H}_2}\overset{|}{\mathrm{C}}\mathrm{=CH}-$), 6.95 (1 H, t, J = 2 Hz, $\mathrm{ClCH_2}\overset{|}{\mathrm{C}}\mathrm{=C\underline{H}CO_2}-$).

Diels–Alder reaction of 1-*vinylcyclohexene* **3** *with chloromethylmaleic anhydride* **2b**. A solution of 1-vinylcyclohexene (1.5 g 13, 9 mmoles) and chloromethylmaleic anhydride **2b** (2.0 g, 13.65 mmoles) in dioxane (2 ml) containing a small amount of hydroquinone was heated in a sealed tube at 70° for 23 h. Evaporation of the solvent left a crystalline product (2.5 g) which was recrystallized from *n*-hexane to afford the adduct **23**, m.p. 113°. IR: 1860, 1785, 1210, 1005, 945, 925, 915, 810, 805, 785 cm^{-1}. NMR: 3.45, 4.05 (2 H, AB q, J = 12 Hz, $-\mathrm{CH_2Cl}$), 3.64 (1 H, dd, J = 2, 9 Hz, $-\mathrm{CH_2}\overset{|}{\mathrm{C}}\mathrm{\underline{H}CO_2}-$), 5.37 (1 H, m, $-\overset{|}{\mathrm{C}}\mathrm{=C\underline{H}CH_2}-$); ($C_5H_5N$): 3.64, 4.20 (2 H, AB q, J = 11 Hz, $-\mathrm{CH_2Cl}$). (Found: C, 61.35; H, 5.86. $C_{13}H_{15}O_3Cl$ requires: C, 61.29; H, 5.95%). Adduct **23** (111 mg) was stirred overnight at room temp with Zn dust (1.04 g) and NaI (300 mg) in AcOH (4.5 ml). Additional Zn(1.0 g) was added and the mixture was stirred overnight at 80–90°. The product obtained by usual work-up was chromatographed on a SiO_2–gel column giving crystals, m.p. 97–98° (from *n*-hexane), which were identical with those of adduct **24**.

OsO_4 Oxidation of adduct **23**. To a solution of the adduct (255 mg, 1 mmole) in ether (5 ml) was added a solution of OsO_4 (280 mg, 1.1 mmoles) and pyridine (0.2 ml, 2.53 mmoles) in ether (10 ml). After the mixture had been stirred at room temp for 5 h, it was saturated with H_2S gas. The black precipitate was removed by filtration with the aid of a celite layer and washed with THF. The combined filtrate and washing were evaporated giving a viscous oil (310 mg) which was chromatographed on a column of SiO_2–gel (7 g). Recrystallization of the $CHCl_3$ eluate (209 mg, 72.3% yield) from anhyd benzene afforded the *cis*-diol **25**, m.p. 155–156°. IR: 3600 (sh), 3540, 1840, 1765, 1210, 1190, 1050, 970, 945 cm^{-1}. NMR (C_5D_5N): 2.11 (1 H, dd, J = 2, 12 Hz, $-\mathrm{CH_2}\overset{|}{\mathrm{C}}\mathrm{\underline{H}}-$), 2.42 (1 H, dd, J = 7.5, 11, 14 Hz, $=\mathrm{CHCH_\alpha\underline{H}_\beta}\overset{|}{\mathrm{C}}\mathrm{H}-$), 2.72 (1 H, ddd, J = 2, 5.5, 14 Hz, $=\mathrm{CHC\underline{H}_\alpha H_\beta}\overset{|}{\mathrm{C}}\mathrm{H}-$), 3.13 (1 H, br d, J = 7.5 Hz, $-\mathrm{CH_2}\overset{|}{\mathrm{C}}\mathrm{\underline{H}CO_2}-$), 4.32 (1 H, dd, J = 5.5, 11 Hz, $-\mathrm{C\underline{H}OHCH_2}-$), 4.31, 5.09 (2 H, AB q, J = 11 Hz, $-\mathrm{CH_2Cl}$). (Found: C, 54.45; H, 5.97. $C_{13}H_{17}O_5Cl$ requires: C, 54.07; H, 5.95%).

Diels–Alder reaction of 1-*vinylcyclohexene* **3** *with citraconic anhydride* **2c**. A mixture of 1-vinylcyclohexene (1.08 g), 10 mmoles), citraconic anhydride **2c** (1.12 g, 10 mmoles) and a small amount of hydroquinone were sealed in a glass tube and heated at 65° for 24 h. The reaction mixture was chromatographed on a SiO_2–gel column and elution with $CHCl_3$ gave crystals (1.04 g, 47.3% yield), which were recrystallized from *n*-hexane giving pure adduct **24**, m.p. 98–99°. IR: 1855, 1835, 1780, 1640–1660 (br), 1225, 1175, 1160, 1005, 955, 943, 905, 820, 805, 745 cm^{-1}. NMR: 1.43 (3 H, s, $\gt\!\mathrm{CMe}$), 2.70 (1 H, ddd, J = 2. 5, 18 Hz, $-\mathrm{C\underline{H}_\alpha H_\beta}\overset{|}{\mathrm{C}}\mathrm{HCO_2}-$), 2.92 (1 H, dd, J = 2, 8 Hz, $-\mathrm{CH_2}\overset{|}{\mathrm{C}}\mathrm{\underline{H}CO_2}-$), 5.37 (1 H, br d, J = 4 Hz, $-\overset{|}{\mathrm{C}}\mathrm{=C\underline{H}CH_2}-$). (Found: C, 70.85; H, 7.35. $C_{13}H_{16}O_3$ requires: C, 70.89; H, 7.32%).

Conversion of Diels–Alder adduct **24** *into* 1-*methylnaphthalene*. Adduct **24** was warmed in a water bath with aq $NaHCO_3$ solution until it was completely dissolved. Acidification with dil HCl and extraction with ether furnished the corresponding dicarboxylic acid as an amorphous powder. This acid (238 mg, 1 mmole) was treated with $Pb(OAc)_4$ (532 mg, 1.2 mmoles) and pyridine (0.12 ml) in dry benzene (1.73 ml) under refluxing for 3.5 h. The resulting white precipitate was removed by filtration and the filtrate was washed with H_2O, dil HCl, aq $NaHCO_3$ and sat NaCl, then dried over $MgSO_4$. Evaporation of the solvent afforded 82 mg of mobile oil with a characteristic hydrocarbon odor. This product was heated with 30% Pd-on-charcoal at 300° for 2 h. Removal of the catalyst furnished 46 mg of a light yellow oil which was filtered through a column of Al_2O_3 (Woelm, basic). Elution with petroleum ether-benzene (4:1) gave 1-methylnaphthalene (46 mg) as a colorless oil. The IR spectrum was superimposable on that of authentic sample and the m.p. of the derived pictrate (orange needles, m.p. 139–140.5°) was not depressed when it was mixed with authentic specimen.

OsO_4 Oxidation of adduct **24**. The diels–Alder adduct **24**

(220 mg, 1 mmole) was oxidized with OsO_4 in the same way as **23**. Crude crystals (120 mg, 47.2% yield) obtained after chromatographic purification were recrystallized from dry benzene to afford the diol **26** as pure crystals, m.p. 156–157°. IR: 3520, 1840, 1760, 1220, 1200, 1185, 1055, 975, 965, 955, 940, 885 cm^{-1}. NMR ($CDCl_3:C_5D_5N = 7:1$): 1.76 (3 H, s, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{Me}$), 2.22 (1 H, ddd, J = 7, 11, 14 Hz, $-\overset{|}{\mathrm{C}}\mathrm{HCH_{\alpha}\underline{H}_{\beta}}\overset{|}{\mathrm{C}}\mathrm{H}-$), 2.39 (1 H, ddd, J = 2, 6, 14 Hz, $-\overset{|}{\mathrm{C}}\mathrm{HC\underline{H}_{\alpha}H_{\beta}}\overset{|}{\mathrm{C}}\mathrm{H}-$), 3.04 (1 H, dd, J = 2, 7 Hz, $-\mathrm{CH_{\alpha}H_{\beta}}\overset{|}{\mathrm{C}}\mathrm{\underline{H}CO_2}-$), 4.02 (1 H, dd, J = 6, 11 Hz, $-\mathrm{CH_{\alpha}H_{\beta}C\underline{H}OH}-$). (Found: C, 61.47; H, 7.15. $C_{13}H_{18}O_5$ requires: C, 61.40; H, 7.1J%).

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