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89. Proof of the Absolute Configuration of (−)-(*S*)-2-Hydroxy-β-ionone by Correlation with Ursolic Acid and with (−)-*trans*-Verbenol

by **Sina Escher, Wolfgang Giersch** and **Günther Ohloff**

Firmenich SA, Research Laboratories, CH-1211 Geneva 8

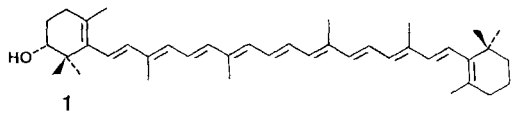
Dedicated to Prof. *Conrad Hans Eugster* on the occasion of his 60th birthday

(16.II.81)

Summary

(−)-(*S*)-2-Hydroxy-β-ionone (**33**), (+)-(2*S*,6*S*)-2-hydroxy-α-ionone (**34**), and their acetates **35** and **36** have been synthesized from (+)-(*S*)-6-methylbicyclo[4.3.0]-non-1-ene-3,7-dione (**3**). The key intermediate (+)-(1*R*,3*S*,6*S*)-2,2,6-trimethyl-7-oxobicyclo[4.3.0]non-3-yl acetate (**7**) was correlated with a degradation product of the pentacyclic triterpene ursolic acid (**16**). Compound **33** was also synthesized by an alternative route starting from (−)-*trans*-verbenol (**42**).

The pigment of the green freshwater alga *Trentepholia isolithus* (L.) *Wallroth* consists of a mixture of carotenoids which include 2-hydroxylated derivatives such as β,β-caroten-2-ol (**1**), β,ε-caroten-2-ol and β,β-carotene-2,2′-diol, the first such compounds isolated from natural sources [1]. On the basis of circular dichroism measurements and use of a modification of *Horeau*'s method the (*R*)-configuration has been proposed for the chiral centre in compound **1** [1] [2]. However, direct chemical proof of this has not been presented so far; and we now describe two separate approaches designed to provide such proof. The main object of these



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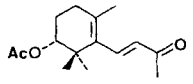

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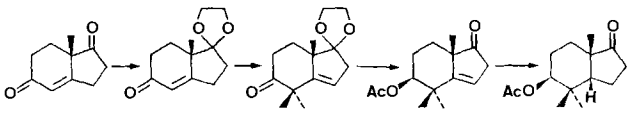
was the stereochemically unambiguous synthesis of an optically active 2-acetoxy-β-ionone, the enantiomer **2** having been obtained by oxidative degradation of compound **1** [2]. We describe the synthesis of its mirror image, (−)-(*S*)-2-acetoxy-β-ionone (**35**), and of the parent alcohol **33** (s. below).

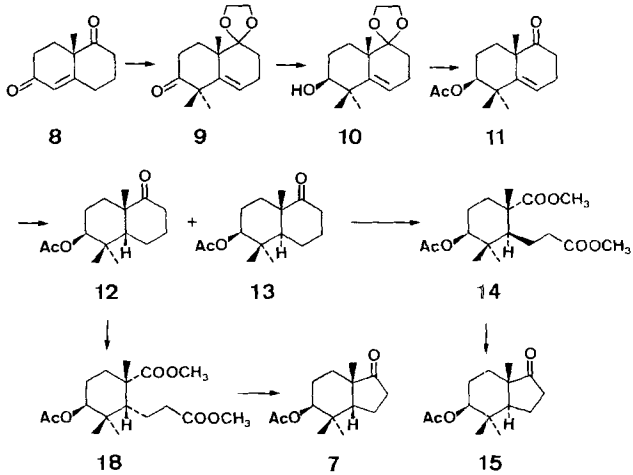


3 4 5 6 7

A key intermediate for this was the (+)-(1*R*,3*S*,6*S*)-keto acetate **7**, which was obtained from the bicyclic (+)-(*S*)-diketone **3**. The latter was readily available in high optical purity by the method of *Eder et al.* [3] and *Hajos et al.* [4a–b]. Following a previously described sequence [5] diketone **3** was selectively protected by an acetal group [6] to give the ethylenedioxy-enone **4** which in turn was dialkylated using potassium *t*-butoxide and methyl iodide [7] to yield compound **5**. Reduction with lithium aluminium hydride, followed by acetal cleavage and acetylation led to keto acetate **6**. Catalytic hydrogenation of this gave the desired intermediate **7** as the sole product.

Throughout this sequence the absolute configuration at C(6) remains unchanged. The newly formed chiral centres at C(1) and C(3) are present also in the compounds **33** and **34** (s. below), and hence their configuration had to be proven unequivocally. For this we decided to rely neither on arguments based on interpretation of spectroscopic or chiroptical data nor on trying to rationalize the stereoselectivity and course of the reactions leading to compounds **6** and **7**, but to establish a direct chemical correlation between compound **7** and a natural product of established absolute configuration.

To this end we converted the *Wieland-Miescher* ketone **8**[1]) of (*S*)-configuration [8] [9] into compound **9** by the route described above [5]. Reduction of **9** with lithium aluminium hydride led in our hands[2]) to a single alcohol **10** which, by removal of the acetal group and acetylation, gave a single keto acetate **11**. Catalytic hydrogenation of **11** was slow and yielded the two C(1)-epimeric products **12** and **13**



8 9 10 11

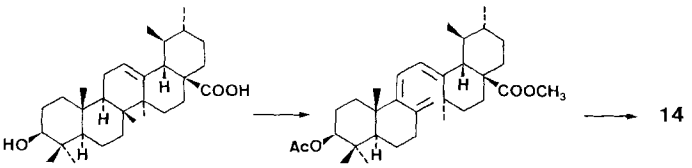
12 13 14

18 7 15

[1]) The optical purity of **8** was *ca.* 60%.

[2]) *Kalvoda & Loeffel* [5] obtained a *ca.* 1:1 mixture of epimeric alcohols in this reduction.

which were separated by chromatography. Oxidative cleavage [10] [11] of the *trans*-decaline derivative **13** led to the triester **14**, identical with a product which we obtained by classical degradation methods [12] [13] from ring A of ursolic acid (**16**) [14] [15] *via* the tetracyclic triene diester **17**, except that the synthetic product showed $[\alpha]_D^{20} = -6°$ while the degradation product had $[\alpha]_D^{20} = -10°$; the

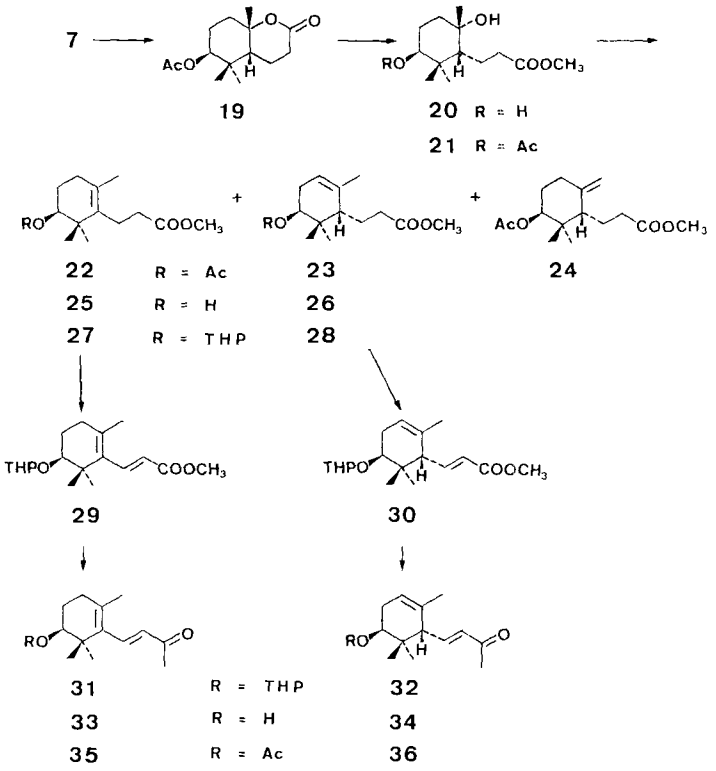


60% optical purity is clearly a consequence of the optical purity of starting material **8**[1]). Synthetic triester **14** was now subjected to *Dieckmann* condensation followed by hydrolysis, decarboxylation and reacetylation [10]. The resulting (+)-(1*S*,3*S*,6*S*)-keto acetate **15** was a diastereoisomer of compound **7**. On the other hand, when the *cis*-decaline derivative **12** was subjected to the same reaction sequence *via* triester **18**, the resulting (+)-(1*R*,3*S*,6*S*)-keto acetate was identical in all respects (except for the expected lower optical rotation) with compound **7** originally formed from compound **3**[3]).

Having thus proved the absolute configuration of intermediate **7** beyond doubt we could now proceed with the synthesis of our target compounds. Keto acetate **7** obtained by the synthetic route[3]) was subjected to *Baeyer-Villiger* oxidation [16], and the lactone **19** thus obtained was converted into the dihydroxy ester **20**. Treatment of its monoacetate **21** with thionyl chloride in pyridine at 0° led to dehydration of the tertiary hydroxyl group and production of three isomeric olefins **22**–**24** in the ratio 6:3:1, separable by column chromatography. Compounds **22** and **23** were each subjected to base-catalyzed methanolysis, giving the hydroxy esters **25** and **26**, respectively, which were in turn converted into their tetrahydropyranyl ethers **27** and **28**. Formation of the corresponding α-phenylseleno esters and oxidative elimination [17] led to the doubly unsaturated esters **29** and **30**. The conversion of these esters into the corresponding methyl ketones **31** and **32** was achieved in both cases *via* the following steps: lithium aluminium hydride reduction to the primary allylic alcohol, manganese dioxide oxidation to the aldehyde, treatment with methyllithium to give a secondary allylic alcohol which was again oxidized with manganese dioxide. Removal of the protective group in **31** led to (−)-(*S*)-2-hydroxy-β-ionone (**33**, $[\alpha]_D^{20} = -32°$), whose acetylation gave (+)-(*S*)-2-acetoxy-β-ionone (**35**) with $[\alpha]_D^{20} = +10°$[4]). This product was identical in all respects (including chirality) with a (+)-2-acetoxy-β-ionone of $[\alpha]_D^{23} = +8°$ which had previously been obtained by *Ito et al.* [19] by enzymatic reduction of 2-oxo-

[3]) Optical purity of **7** from **3** ≥ 97%.

[4]) *Mikami et al.* [18] have also obtained compound **33** by microbiological hydroxylation of β-ionone. Though the specific rotation they reported for its acetate **35** ($[\alpha]_{589}^{23} = +7.12°$) is close to the value shown by our product, the alcohol **33** was in [18] only of $[\alpha]_D^{23} = -11.3°$. We have no explanation for this discrepancy.

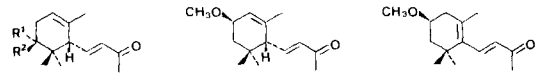


β-ionone, and which was used for the synthesis of a β,β-caroten-2-ol, shown to be the enantiomer of the naturally occurring compound **1** [19]. Hence, our synthetic sequence constitutes full confirmation of the absolute configurations of compounds **1** and **2** as previously deduced by physical methods alone [1] [2].

From the unsaturated ketone **32** we obtained in the same way the (so far unknown) (+)-(2*S*,6*S*)-2-hydroxy-α-ionone (**34**; $[\alpha]_D^{20} = +396°$), and its acetate **36** ($[\alpha]_D^{20} = +326°$). Attempts to epimerize at the chiral centre C(6) of **32** [20] [21] were unsuccessful.

Intermediate **24** might have served as starting material for the corresponding γ-ionone derivatives, but unfortunately it was obtained in too small amounts for that purpose.

The CD. curves of **34** [$\Delta\varepsilon$ (239 nm) = +17.5, $\Delta\varepsilon$ (312 nm) = −1.10] and **36** [$\Delta\varepsilon$ (236 nm) = +17.8, $\Delta\varepsilon$ (318 nm) = −1.14] are similar to those reported for (+)-(*R*)-α-ionone (**37**) [22], (+)-(2*R*,6*R*)-α-irone (**38**) [21], (+)-(2*S*,6*R*)-α-irone (**39**) [21], and (+)-(3*R*,6*R*)-3-methoxy-α-ionone (**40**) [23]. These compounds have in common a 3-(3′-oxo-1′-butenyl)cyclohexene system of (*P*)-helicity. The substituent at C(2) or C(3) of the ionone or irone skeleton has virtually no influence on the *Cotton* effect. The band at 239 nm (for **34**) and 236 nm (for **36**) is attributed to the chiral interaction of the electronic transition moments of the olefin and the enone chromophore [24]. Such interaction occurs only if the enone side chain is preferentially in the pseudoaxial conformation. Consequently, the C(2) substituent in **34** and **36** must be equatorial. This is clearly the case as shown by the ^{1}H-NMR. spectra, where the axial H–C(2) resonates as $d \times d$ with coupling constants of 6 and 8 Hz (in **34**), and 6 and 10 Hz (in **36**), respectively.



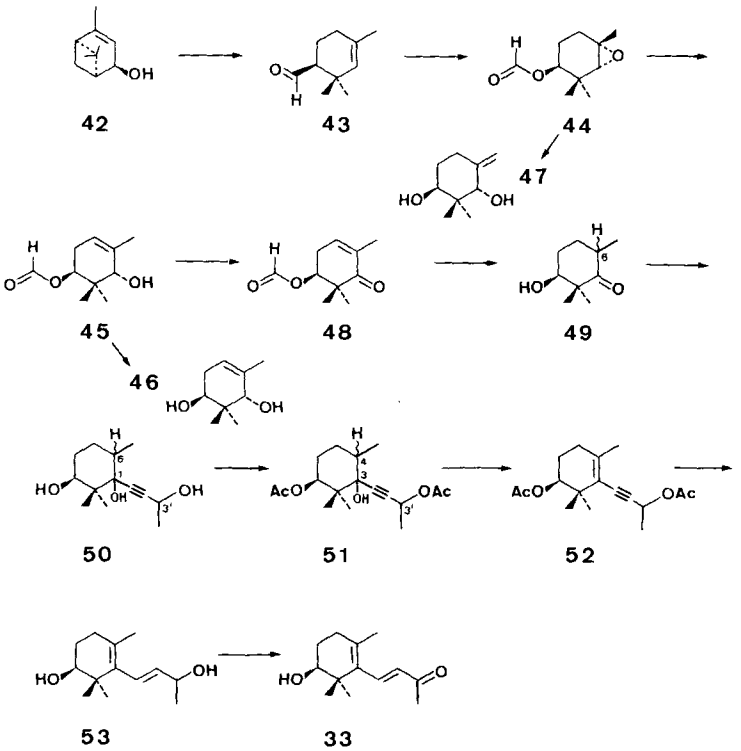
37 R^1, R^2 = H **40** **41**

38 R^1 = CH_3, R^2 = H

39 R^1 = H, R^2 = CH_3

(−)-(*S*)-2-Hydroxy-*β*-ionone (**33**) gives rise to very weak *Cotton* effects [$\Delta\varepsilon$ (279 nm) = +0.19, $\Delta\varepsilon$ (315 nm) = −0.14, $\Delta\varepsilon$ (355 nm) < +0.02]. The curve is related to that of (+)-(3*R*)-3-methoxy-*β*-ionone (**41**) [23], both compounds being 4-hydroxycyclohexenes of (*P*)-helicity. The CD. spectrum of **35** [$\Delta\varepsilon$ (279 nm) = +0.22, $\Delta\varepsilon$ (320 nm) ≪ −0.02] is enantiomeric with that of **2**. The lower energy band of the spectrum of **35** is leveled out whereas the one of **2** is reported to be 'weakly positive' [2].

A more direct asymmetric synthesis of compound **33** was suggested by the ready availability of (−)-(*S*)-2,2,4-trimethyl-3-cyclohexene-1-carbaldehyde (**43**) by pyrolysis of (−)-*trans*-verbenol (**42**) [25], a reaction which appears to proceed *via* *trans*-chrysanthenol [26]. Reaction of **43** with *m*-chloroperbenzoic acid at room temperature for several days gave the epoxy formate **44** in 33% yield. This epoxide underwent rearrangement to the allylic alcohol **45** in almost quantitative yield by the action of the acid clay FILTROL® in dioxane. Hydrolysis of **45** led to diol **46**. The isomeric diol **47** with an exocyclic double bond was formed when epoxide **44** was rearranged by the action of lithium diethylamide (with concurrent hydrolysis of the formate group). The *trans*-relationship of the two oxygen functions in compounds **44** and **45** is indicated by the fact that in both diols **46** and **47** there is no



42 **43** **44** **47** **45** **48** **49** **46** **50** **51** **52** **53** **33**

indication of intramolecular hydrogen bonding in the IR. spectrum. Compound **45** was then oxidized with chromium trioxide/pyridine to give the ketone **48**. Hydrolysis of **48** followed by catalytic hydrogenation led to a 1:1 mixture of C(6)-epimeric hydroxy ketones **49**. The latter was treated with the *Grignard* reagent derived from 3-butyn-2-ol [27] to give the triol **50**[5]) in 73% yield. After selective acetylation (acetic anhydride/pyridine at RT.) the diacetate **51**[6]) underwent dehydration on heating with phosphoryl chloride in pyridine to give en-yne **52** in 43% yield.

Reduction of **52** with lithium aluminium hydride under forcing conditions led to 2-hydroxy-β-ionol (**53**) whose oxidation with active manganese dioxide gave (−)-(*S*)-2-hydroxy-β-ionone (**33**). This showed $[\alpha]_D^{20} = -8°$, corresponding to only *ca.* 25% optical purity. The starting material (−)-*trans*-verbenol (**42**) had $[\alpha]_D^{20} = -101°$ corresponding to 60% optical purity [28], and thus our synthetic route **42**→**33** involved considerable loss of chiral integrity. We have not investigated this further but believe that a careful study of the pyrolysis of **42** as well as of the *Baeyer-Villiger* oxidation of **43** may provide an explanation.

We should like to express our gratitude to Dr. *D. Felix*, ETH Zurich, for the circular dichroism data, to Dr. *W. Acklin*, ETH Zurich, for information on ursolic acid, and to Mr. *Y. Niclass* and Mr. *P. Fantini* who performed the experimental work with great skill and care.

Experimental Part[7])

1. Synthesis of the 2-hydroxyionones 33 and 34 from compound 3. – 1.1. *Synthesis of (+)-(S)-6-methylbicyclo[4.3.0]non-1-ene-3,7-dione* (**3**). Diketone **3** was prepared according to [4b]; m.p. 64.5 to 66.5°, $[\alpha]_D^{20} = +358°$ ($c = 1.01$, benzene), optical purity ≥ 97%.

1.2. *Synthesis of (+)-(S)-7,7-ethylenedioxy-6-methylbicyclo[4.3.0]non-1-en-3-one* (**4**). The procedure was adopted from [6]. A mixture of **3** (70.5 g, 430 mmol), 2-ethyl-2-methyl-1,3-dioxolane (280 ml), ethylene glycol (5.6 ml) and *p*-toluenesulfonic acid (1.4 g) was stirred at RT. The formation of **4** was followed by GLC. *(SOMB)*. After 5 days, the mixture contained *ca.* 80% of **4**. It was neutralized with triethylamine and evaporated (RV.). The residue was taken up in toluene, washed twice with sat. aq. $NaHCO_3$-solution and dried (K_2CO_3). Upon evaporation of the solvent, 88 g of crude **4** were obtained and chromatographed on silica gel (*Merck*, 0.063–0.20 mm, 20-fold amount) with hexane/ethyl acetate 7:3 yielding 45 g (50%) of **4**, purity 90% (GLC.), $[\alpha]_D^{20} = +7°$[8]) ($c = 0.99$, $CHCl_3$). – IR. (liq.): 1670. – ^{1}H-NMR. (60 MHz): 1.22 (*s*, 3 H, H_3C–C(6)); 3.91 (*s*, 4 H, OCH_2CH_2O); 5.74 (*m*, 1 H, H–C(2)). – MS.: 208 (100, M^+), 165 (11), 138 (15), 99 (30), 86 (91), 79 (23), 55 (12), 43 (17).

1.3. *Synthesis of (+)-(S)-7,7-ethylenedioxy-2,2,6-trimethylbicyclo[4.3.0]non-9-en-3-one* (**5**). Ketone **4** (*ca.* 90% pure, 17.16 g, *ca.* 74 mmol) was converted into **5** according to [7]. The crude product was purified by chromatography on 450 g of silica gel with hexane/ether 7:3 yielding 8.86 g (51%) of **5**, $[\alpha]_D^{20} = +49°$ ($c = 0.74$, $CHCl_3$). – IR. (liq.): 1705, 1630. – ^{1}H-NMR. (60 MHz): 1.26 (*s*, 9 H, 2 H_3C–C(2), H_3C–C(6)); 3.96 (*s*, 4 H, OCH_2CH_2O); 5.57 (*m*, 1 H, H–C(9)). – MS.: 236 (57, M^+), 221 (8), 193 (100), 165 (66), 136 (24), 121 (47), 107 (54), 99 (16), 86 (59), 73 (21), 55 (23), 41 (31).

1.4. *Synthesis of (+)-(3S,6S)-2,2,6-trimethyl-7-oxobicyclo[4.3.0]non-9-en-3-yl acetate* (**6**). A solution of **5** (12.73 g, 54 mmol) in anh. ether (110 ml) was added dropwise to a suspension of $LiAlH_4$ (1.10 g, 29 mmol) in 290 ml of anh. ether. The mixture was stirred for 1 h at reflux temp. and 1.5 h at RT., then hydrolyzed by adding water (1.1 ml) followed by 15% aq. NaOH-solution (1.1 ml) and water

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[5]) A mixture of triols diastereoisomeric at C(1), C(6) and C(3′).

[6]) A mixture of diacetates diastereoisomeric at C(3), C(4) and C(3′).

[7]) For general remarks see [29]. Abbreviations: RT. = room temperature, RV. = rotatory evaporator *(Büchi)*, THF = tetrahydrofuran; anh. = anhydrous, aq. = aqueous, br. = broad.

[8]) Sign and value of $[\alpha]_D^{20}$ may be different for a 100% chemically pure sample.

(3.3 ml). The precipitate was filtered off and washed several times with anh. ether. The combined filtrates were evaporated. The residue (13.73 g) was dissolved in acetic acid/water 9:1 (320 ml) and kept at 60° for 1 h. The solution was diluted with water (1.2 l) and extracted with ether (3 times 800 ml). The usual work-up of the ether phase afforded 15 g of a viscous oil which was acetylated with acetic anhydride/pyridine 1:2 (105 ml) at RT. for 3 days. In order to hydrolyze the excess of acetic anhydride the mixture was poured into ice-cold saturated aq. $NaHCO_3$-solution (400 ml) and stirred for 30 min. Extraction with ether and work-up gave 14.3 g of crude **6**. This batch was combined with a previous one (8.16 g, prepared from 8.6 g (36 mmol) of **5**) and purified by chromatography on silica gel (20-fold amount) with hexane/ether 9:1. Impure fractions were rechromatographed using the same solvent system, but on a 100-fold amount of adsorbent. Yield: 10.85 g (51%) of **6**. A small sample was distilled (bulb-to-bulb) at 105–115° (bath)/0.1 Torr, $[\alpha]_D^{20} = +82°$ ($c = 0.74$, $CHCl_3$). – IR. (liq.): 1740, 1245, 1040. – ^{1}H-NMR. (60 MHz): 1.15 and 1.17 (2*s*, 6 H, 2 H_3C–C(2)); 1.30 (*s*, 3 H, H_3C–C(6)); 2.09 (*s*, 3 H, CH_3COO); 2.96 (*m*, 2 H, 2 H–C(8)); 4.49 (*d*×*d*, $J_{3,4} = 8$, $J'_{3,4} = 7$, 1 H, H–C(3)); 5.82 (*t*, $J_{8,9} = 4$, 1 H, H–C(9)). – MS.: 236 (< 1, M^+), 194 (19), 176 (100), 148 (45), 134 (99), 119 (18), 107 (20), 91 (19), 79 (11), 55 (11), 45 (100).

1.5. *Synthesis of (+)-(1R,3S,6S)-2,2,6-trimethyl-7-oxobicyclo[4.3.0]non-3-yl acetate* (**7**). Keto acetate **6** (10.8 g, 45.7 mmol) was hydrogenated in ethanol over 8% of platinum oxide. After H_2 uptake had ceased, the mixture was filtered, the filtrate evaporated and the residue recrystallized from ether/hexane: 7.2 g (66%) of **7**, m.p. 78–81°, $[\alpha]_D^{20} = +41°$ ($c = 0.98$, $CHCl_3$). A small sample was recrystallized several times from ether/hexane, m.p. 84.5–85.5°, $[\alpha]_D^{20} = +41°$ ($c = 0.52$, $CHCl_3$). – IR. ($CHCl_3$): 1720, 1250, 1120, 1080, 1030, 1000, 960. – ^{1}H-NMR. (90 MHz): 0.94 and 1.12 (2*s*, 6 H, 2 H_3C–C(2)); 1.24 (*s*, 3 H, H_3C–C(6)); 2.08 (*s*, 3 H, CH_3COO); 4.86 (distorted *t*, $J_{3,4} = 7$, 1 H, H–C(3)). – MS.: 238 (6, M^+), 196 (< 1), 178 (60), 163 (22), 150 (64), 134 (41), 121 (92), 107 (70), 97 (35), 81 (21), 69 (32), 55 (25), 43 (100).

$C_{14}H_{22}O_3$ (238.32) Calc. C 70.55 H 9.31% Found C 70.51 H 9.33%

1.6. *Synthesis of (+)-(1S,6R,8S)-1,7,7-trimethyl-3-oxo-2-oxabicyclo[4.4.0]dec-8-yl acetate* (**19**). The procedure is similar to the one described in [16]. An ice-cooled mixture of **7** (3.8 g, 16 mmol) and anh. Na_2HPO_4 (10.4 g) in anh. dichloromethane (13 ml) was treated dropwise with 8 ml of a *ca.* 2.5M solution of trifluoroperacetic acid in dichloromethane[9]). The suspension was stirred at RT. Within 2 days more trifluoroperacetic acid solution (16 ml) was added in portions until TLC. analysis indicated the absence of **7**. The mixture was taken up in ether, washed with aq. $NaHSO_3$- and $NaHCO_3$-solutions and dried ($K_2CO_3/MgSO_4$). Upon removal of the solvents, 3.71 g of crude, crystalline product were obtained and combined with 3.77 g derived from an analogous run. Chromatography on silica gel (180 g) with hexane/ethyl acetate 2:1 gave 5.72 g (70%) of **19**, m.p. 125–132°. After several recrystallizations from ether/dichloromethane/hexane, a sample had m.p. 139°, $[\alpha]_D^{20} = +24°$ ($c = 0.82$, $CHCl_3$). – IR. ($CHCl_3$): 1720, 1040. – ^{1}H-NMR. (90 MHz): 0.97 (*s*, 6 H, 2 H_3C–C(7)); 1.45 (*s*, 3 H, H_3C–C(1)); 2.10 (*s*, 3 H, CH_3COO); 2.62 (*m*, 2 H, 2 H–C(4)); 4.75 (*m*, $w_{1/2} = 6$, 1 H, H–C(8)). – MS.: 254 (0, M^+), 239 (< 1), 194 (< 1), 179 (5), 136 (35), 119 (47), 94 (47), 81 (45), 67 (51), 55 (100), 43 (63), 41 (87).

1.7. *Conversion of lactone* **19** *into olefins* **22–24**. Lactone **19** (5.08 g, 20 mmol) was hydrolyzed in 5% aq. KOH-solution/ethanol 3:1 (100 ml) at 60° for 20 h. The solution was acidified with 10% aq. HCl-solution and extracted with ether. The ether layer was washed with sat. NaCl-solution, dried ($MgSO_4$), concentrated to 100 ml and treated with an excess of diazomethane in ether. Removal of the solvent gave 5.5 g of diol **20** which was acetylated in acetic anhydride/pyridine 1:2 (30 ml) at 50° overnight. The usual work-up gave 5.66 g of monoacetate **21**. To a solution of this material in anh. pyridine (50 ml) was added dropwise at 0° freshly distilled thionyl chloride (2.8 ml, 40 mmol). The mixture was stirred at 0° for 1 h and worked up with ether in the usual manner. The crude product (5.0 g) was chromatographed on 150 g of silica gel with hexane/ethyl acetate 85:15. Yield: 4.33 g (80%) of **22–24**. GLC. (*Carbowax 20M* or *SP-1000*): **22**/(**23**+**24**) 2:1; **23** and **24** are eluted before **22**. TLC. (hexane/ether 9:1, 4 developments): Rf of **22** 0.30, Rf of **23** 0.25, and Rf of **24** 0.20.

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[9]) Prepared from 100% hydrogen peroxide (6.12 g, 180 mmol) and trifluoroacetic anhydride (30 ml, 216 mmol) in anh. dichloromethane (30 ml).

The estimated ratio (GLC., TLC.) of **22/23/24** was *ca.* 6:3:1. The isomers were separated preparatively by chromatography on silica gel (100-fold amount) with hexane/ether 9:1. Mixed fractions were rechromatographed under the same conditions. *(−)-(5′S)-Methyl 3-(5′-acetoxy-2′,6′,6-trimethyl-1′-cyclohexenyl)propionate* (**22**): $[\alpha]_D^{20} = -2°$ ($c = 1.15$, EtOH). – IR. (liq.): 1730, 1240, 1015, 1005. – ^{1}H-NMR. (90 MHz): 1.00 (*s*, 6 H, 2 H_3C–C(6′)); 1.62 (*s*, 3 H, H_3C–C(2′)); 2.04 (*s*, 3 H, CH_3COO); 2.35 (*s*, 4 H, 2 H–C(2), 2 H–C(3)); 3.68 (*s*, 3 H, CH_3OOC); 4.74 (*d*×*d*, $J_{4',5'} = 8.5$, $J'_{4',5'} = 5$, 1 H, H–C(5′)). – MS.: 268 (0, M^+), 208 (38), 193 (8), 177 (9), 161 (16), 134 (31), 121 (100), 119 (88), 88 (24), 43 (50).

(+)-(1′S,3′S)-Methyl 3-(5′-acetoxy-2′,6′,6′-trimethyl-2′-cyclohexenyl)propionate (**23**): $[\alpha]_D^{20} = +80°$ ($c = 1.17$, EtOH). – IR. (liq.): 1740, 1250, 1040. – ^{1}H-NMR. (90 MHz): 0.93 (*s*, 6 H, 2 H_3C–C(6′)); 1.71 (*s* with fine structure, 3 H, H_3C–C(2′)); 2.05 (*s*, 3 H, CH_3COO); 2.40 (*m*, 5 H, 2 H–C(2), H–C(1′), 2 H–C(4′)); 3.67 (*s*, 3 H, CH_3OOC); 4.88 (*d*×*d*, $J_{4',5'} = 8.5$, $J'_{4',5'} = 6$, 1 H, H–C(5′)); 5.23 (*m*, 1 H, H–C(3′)). – MS.: 268 (0, M^+), 208 (29), 193 (7), 177 (5), 161 (18), 134 (28), 121 (100), 119 (69), 88 (27), 43 (60).

(+)-(1′S,3′S)-Methyl 3-(3′-acetoxy-2′,2′-dimethyl-6′-methylidenecyclohexyl)propionate (**24**): $[\alpha]_D^{20} = +21°$ ($c = 0.71$, EtOH). – IR. (liq.): 1740, 1250, 1030, 900. – ^{1}H-NMR. (90 MHz): 0.92 and 0.95 (2*s*, 6 H, 2 H_3C–C(2′)); 2.06 (*s*, 3 H, CH_3COO); 3.68 (*s*, 3 H, CH_3OOC); 4.62 and 4.85 (2 *m*, 2 H, H_2C=C(6′)); 4.90 (*d*×*d*, $J_{3',4'} = 9$, $J'_{3',4'} = 5$, 1 H, H–C(3′)). – MS.: 268 (0, M^+), 208 (13), 193 (4), 177 (6), 161 (12), 134 (14), 121 (54), 88 (13), 66 (100), 43 (62).

1.8. *Synthesis of (−)-(5′S)-methyl 3-[2′,6′,6′-trimethyl-5′-(2″-tetrahydropyranyloxy)-1′-cyclohexenyl]-propionate* (**27**)[10]. To a solution of **22** (814 mg, 3 mmol) in anh. methanol (20 ml) was added 1.0 N methanolic CH_3ONa-solution (3 ml), and the solution was left at RT. until TLC. showed the absence of starting material (48 h). The mixture was neutralized with acetic acid and treated with ethereal diazomethane solution. After solvent removal the residue was taken up in ether and worked up in the usual way: 664 mg (97%) of TLC.-homogeneous **25**. This material (640 mg, 2.8 mmol) was dissolved in anh. chloroform (10 ml), and freshly distilled dihydropyran (510 µl, 5.6 mmol) and phosphoryl chloride (3 µl) were added. After 20 h at RT., the usual work-up and chromatography on silica gel gave 793 mg (91%) of **27** as a mixture of diastereoisomers[10]), $[\alpha]_D^{20} = -21°$ ($c = 0.92$, EtOH). – IR. (liq.): 1735, 1025. – ^{1}H-NMR. (90 MHz): 0.97, 1.02 and 1.11 (3*s*, 6 H, 2 H_3C–C(6′)); 1.60 (br.*s*, 3 H, H_3C–C(2′)); 2.35 (*s*, 4 H, 2 H–C(2), 2 H–C(3)); 3.2–4.1 (*m*, 3 H, H–C(5′), CH_2O); 3.68 (*s*, 3 H, CH_3OOC); 4.59 and 4.73 (2 *m*, 1 H, OCHO).

1.9. *Synthesis of (+)-(1′S,5′S)-methyl 3-[2′,6′,6′-trimethyl-5′-(2″-tetrahydropyranyloxy-2′-cyclo-hexenyl]propionate* (**28**)[10]. From 560 mg (2.1 mmol) of **23** a mixture of diastereoisomers **28**[10]) was prepared in the same way as above. Yield: 480 mg (73%), $[\alpha]_D^{20} = +91°$ ($c = 1.46$, EtOH). – IR. (liq.): 1740, 1035. – ^{1}H-NMR. (90 MHz): 0.87, 0.89, 0.95 and 1.05 (4*s*, 6 H, 2 H_3C–C(6′)); 1.67 (*m*, 3 H, H_3C–C(2′)); 2.35 (*t*, $J_{2,3} = 7$, 2 H, 2 H–C(2)); 3.3–4.05 (*m*, 3 H, H–C(5′), CH_2O); 3.66 (*s*, 3 H, CH_3OOC); 4.55 and 4.71 (2 *m*, 1 H, OCHO); 5.23 (*m*, 1 H, H–C(3′)).

1.10. *Synthesis of (−)-(5′S,2E)-methyl 3-[2′,6′,6′-trimethyl-5′-(2″-tetrahydropyranyloxy)-1′-cyclo-hexenyl]-2-propenoate* (**29**)[10]. The following procedure was adopted from [17]. A flame-dried 25-ml flask equipped with rubber septum, stirring bar and Ar inlet was charged with anh. diisopropylamine (465 µl, 3.3 mmol) and anh. THF (3.3 ml) and cooled to −78°. Butyllithium/hexane (1.7 N, 2 ml, 3.4 mmol) was added. After 20 min at −78°, a solution of **27** (920 mg, 2.97 mmol) in THF (2.5 ml) was added, and the mixture was stirred at −78° for 30 min. A solution prepared from diphenyl-diselenide (515 mg, 1.65 mmol) and bromine (85 µl, 1.65 mmol) in THF (2.3 ml) was then added quickly and the dry ice/2-propanol bath was replaced by an ice bath. Water (1.65 ml), acetic acid (0.33 ml) and 35% H_2O_2-solution (1.32 g) were added, and the mixture was allowed to come to RT. After 90 min, the mixture was worked up and the product isolated with ether. Chromatography on silica gel (90 g) with hexane/ether 9:1 gave 90 mg of mixed fractions (**27** and **29**), and 700 mg (76%) of pure **29**, $[\alpha]_D^{20} = -12°$ ($c = 0.74$, EtOH). – IR. (liq.): 1720, 1620, 1260, 1160, 1025, 860. – ^{1}H-NMR. (90 MHz): 1.06, 1.11 and 1.15 (3*s*, 6 H, 2 H_3C–C(6′)); 1.74 (*s*, 3 H, H_3C–C(2′)); 3.25–4.10 (*m*, 3 H, H–C(5′), CH_2O); 3.78 (*s*, 3 H, CH_3OOC); 4.63 and 4.77 (2 *m*, 1 H, OCHO); 5.83 (*d*, $J_{2,3} = 16$, 1 H, H–C(2)); 7.38 (*d*, $J_{2,3} = 16$, $w_{1/2} = 4$, 1 H, H–C(3)).

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[10]) Epimeric mixture with respect to C(2″).

1.11. *Synthesis of (+)-(1'S,5'S,2E)-methyl 3-[2',6',6'-trimethyl-5'-(2''-tetrahydropyranyloxy)-2'-cyclohexenyl]-2-propenoate* (**30**)[10]. Ester **28** (600 mg, 1.94 mmol) was converted into **30** as described for **27**→**29**. Yield: 414 mg (69%), $[\alpha]_D^{20} = +261°$ ($c = 0.95$, EtOH). – IR. (liq.): 1725, 1645, 1270, 1035, 920, 865, 820. – ^{1}H-NMR. (90 MHz): 0.89, 0.94 and 0.97 (3 *s*, 6 H, 2 H_3C–C(6')); 1.68 (br. *s*, 3 H, H_3C–C(2')); 3.3–4.0 (*m*, 3 H, H–C(5'), CH_2O); 4.55 and 4.74 (2 *m*, 1 H, OCHO); 5.32 (*m*, 1 H, H–C(3')); 5.82 (*d*, $J_{2,3} = 15$, 1 H, H–C(2)); 6.83 (*d*×*d*, $J_{2,3} = 15$, $J_{1',3} = 10$, 1 H, H–C(3)).

1.12. *Synthesis of (−)-(2S)-2-(2'-tetrahydropyranyloxy)-β-ionone* (**31**)[11]. A solution of **29** (700 mg, 2.27 mmol) in anh. ether (11 ml) was added dropwise to a suspension of anh. aluminium trichloride (218 mg, 1.63 mmol) and $LiAlH_4$ (205 mg, 5.40 mmol) in ether (11 ml) at −20°. After stirring at −20° for 1 h, the mixture was cooled to −78°, quenched with methanol (1.15 ml) and poured into saturated aq. NH_4Cl-solution. Usual work-up with ether gave 640 mg of crude allylic alcohol which was oxidized by stirring with activated manganese dioxide (6.4 g) in anh. dichloromethane (30 ml). Filtration and concentration of the filtrate gave 490 mg (1.76 mmol) of crude aldehyde. This was dissolved in anh. ether, methyllithium/ether (0.95 N, 4 ml, 3.90 mmol) was added and the whole left at 0° for 35 min. The mixture was then hydrolyzed with aq. NH_4Cl-solution and worked up with ether in the usual manner, giving 550 mg of alcohol. Oxidation of the latter with manganese dioxide (5.5 g) in dichloromethane (30 ml) and chromatography of the crude product on 40 g of silica gel with hexane/ether 4:1 gave 333 mg (50%) of TLC.-homogeneous **31**[11]), $[\alpha]_D^{20} = -10°$ ($c = 1.00$, EtOH). – IR. (liq.): 1670, 1610, 1260, 1140, 1130, 1080, 1035, 985, 880, 820. – ^{1}H-NMR. (90 MHz): 1.07, 1.12 and 1.16 (3 *s*, 6 H, 2 H_3C–C(1)); 1.76 (*s*, 3 H, H_3C–C(5)); 2.31 (*s*, 3 H, 3 H–C(10)); 3.2–3.7 (*m*, 2 H, CH_2O); 3.94 (*m*, 1 H, H–C(2)); 4.62 and 4.76 (2 *m*, 1 H, OCHO); 6.09 (*d*, $J_{7,8} = 16$, 1 H, H–C(8)); 7.20 (*d*, $J_{7,8} = 16$, $w_{1/2} = 6$, 1 H, H–C(7)).

1.13. *Synthesis of (+)-(2S,6S)-2-(2'-tetrahydropyranyloxy)-α-ionone* (**32**)[11]). Ketone **32** was obtained from **30** (400 mg, 1.30 mmol) as described for **29**→**31**. Yield: 217 mg (57%), $[\alpha]_D^{20} = +318°$ ($c = 0.90$, EtOH). – IR. (liq.): 1675, 1620, 1255, 1035, 990, 920, 870, 820. – ^{1}H-NMR. (90 MHz): 0.90, 0.96 and 1.00 (3 *s*, 6 H, 2 H_3C–C(1)); 1.60 (*s*, 3 H, H_3C–C(5)); 2.28 (*s*, 3 H, 3 H–C(10)); 3.3–4.1 (*m*, 3 H, H–C(2), CH_2O); 4.58 and 4.76 (2 *m*, 1 H, OCHO); 5.42 (*m*, 1 H, H–C(4)); 6.07 (*d*, $J_{7,8} = 15$, 1 H, H–C(8)); 6.67 (*d*×*d*, $J_{7,8} = 15$, $J_{6,7} = 10$, 1 H, H–C(7)).

1.14. *Synthesis of (−)-(S)-2-hydroxy-β-ionone* (**33**). Ether **31** (315 mg, 1.08 mmol) was cleaved in acetic acid/THF/water 3:1:1 (3 ml) at 40° for 4 h. The usual work-up with ether afforded 274 mg of **33** which was chromatographed on 30 g of silica gel with hexane/ethyl acetate 4:1. Yield of TLC.- and GLC.-homogeneous (*SOMB, Carbowax 20 M*) **33**: 199 mg (88%). A sample was distilled (bulb-to-bulb) at 125° (bath)/0.05 Torr, $[\alpha]_D^{20} = -32°$ ($c = 1.04$, EtOH). – UV. (EtOH): 293 (9300). – CD. ($c = 8.4 \cdot 10^{-5}$ mol · l^{-1}, EtOH): $[\theta]_{<246}$ = negative, $[\theta]_{246} = 0$, $[\theta]_{279} = 628$, $[\theta]_{300} = 0$, $[\theta]_{315} = -471$, $[\theta]_{347} = 0$. – IR. (liq.): 3450, 1660, 1600, 1260, 1040, 1000, 980. – ^{1}H-NMR. (90 MHz): 1.07 and 1.11 (2 *s*, 6 H, 2 H_3C–C(1)); 1.75 (*m*, 3 H, H_3C–C(5)); 1.80 (HO); 2.20 (*t*, $J_{3,4} = 6$, 2 H, 2 H–C(4)); 2.30 (*s*, 3 H, 3 H–C(10)); 3.66 (*d*×*d*, $J_{2,3\,ax} = 8$, $J_{2,3\,eq} = 4$, 1 H, H–C(2)); 6.09 (*d*, $J_{7,8} = 16$, 1 H, H–C(8)); 7.20 (*d*, $J_{7,8} = 16$, $w_{1/2} = 4$, 1 H, H–C(7)). – MS.: 208 (9, M^+), 193 (100), 190 (7), 175 (55), 157 (5), 149 (35), 133 (7), 121 (47), 105 (26), 91 (23), 77 (12), 65 (4), 55 (12), 43 (96).

1.15. *Synthesis of (+)-(2S,6S)-2-hydroxy-α-ionone* (**34**). As described above 194 mg (0.66 mmol) of **32** were converted into **34**. Yield after chromatography: 85 mg (62%). For analytical purposes a sample was distilled (bulb-to-bulb) at 130° (bath)/0.05 Torr, $[\alpha]_D^{20} = +396°$ ($c = 0.77$, EtOH). – UV. (EtOH): 228 (14,000). – CD. ($c = 6.35 \cdot 10^{-5}$ mol · l^{-1}, EtOH): $[\theta]_{239} = 57{,}700$, $[\theta]_{287} = 0$, $[\theta]_{312} = -3640$, $[\theta]_{365} = 0$. – IR. (liq.): 3450, 1670, 1620, 1260, 1050, 820. – ^{1}H-NMR. (90 MHz): 0.92 (*s*, 6 H, 2 H_3C–C(1)); 1.45 (HO); 1.68 (*m*, 3 H, H_3C–C(5)); 2.25 (*s*, 3 H, 3 H–C(10)); 2.53 (*d*, $J_{6,7} = 10$, 1 H, H–C(6)); 3.69 (*d*×*d*, $J_{2,3} = 8$, $J'_{2,3} = 6$, 1 H, H–C(2)); 5.42 (*m*, 1 H, H–C(4)); 6.05 (*d*, $J_{7,8} = 16$, 1 H, H–C(8)); 6.63 (*d*×*d*, $J_{7,8} = 16$, $J_{6,7} = 10$, 1 H, H–C(7)). – MS.: 208 (4, M^+), 193 (9), 190 (15), 175 (52), 157 (6), 147 (20), 137 (34), 121 (43), 109 (13), 93 (40), 72 (20), 55 (14), 43 (100).

1.16. *Synthesis of (+)-(S)-2-acetoxy-β-ionone* (**35**). Crude **33** (180 mg, obtained from 0.72 mmol of **31**) was dissolved in acetic anhydride/pyridine 1:2 (1.8 ml) at RT. and left overnight. Work-up with ether and chromatography on 40 g of silica gel with hexane/ether 85:15 afforded 121 mg (67%) of TLC.- and GLC.-homogeneous **35**. A sample was distilled (bulb-to-bulb) at 100° (bath)/0.1 Torr,

[11]) Epimeric mixture with respect to C(2').

$[\alpha]_D^{20} = +10°$ ($c = 1.00$, EtOH). – UV. (EtOH): 291 (8800). – CD. ($c = 1.26 \cdot 10^{-4}$ mol · l^{-1}, EtOH): $[\theta]_{<243}$ = negative, $[\theta]_{243} = 0$, $[\theta]_{279} = 733$, $[\theta]_{310} = 0$, $[\theta]_{320}$ = weakly negative, $[\theta]_{330} = 0$. – IR. (liq.): 1730, 1690, 1670, 1240, 1030, 985. – ^{1}H-NMR. (90 MHz): 1.10 (*s*, 6 H, 2 H_3C–C(1)); 1.78 (br. *s*, 3 H, H_3C–C(5)); 2.09 (*s*, 3 H, CH_3COO); 2.32 (*s*, 3 H, 3 H–C(10)); 4.81 (*d* × *d*, $J_{2,3ax} = 7$, $J_{2,3eq} = 4$, 1 H, H–C(2)); 6.11 (*d*, $J_{7,8} = 16$, 1 H, H–C(8)); 7.19 (*d*, $J_{7,8} = 16$, $w_{1/2} = 5$, 1 H, H–C(7)). – MS.: 250 (6, M^+), 235 (25), 190 (10), 175 (89), 157 (12), 147 (34), 133 (12), 121 (11), 105 (15), 91 (11), 77 (7), 55 (12), 43 (100).

1.17. *Synthesis of (+)-(2S,6S)-2-acetoxy-α-ionone* (**36**). As above 60 mg of crude **34** were acetylated and purified to give 50 mg of **36** which was distilled (bulb-to-bulb) at 90° (bath)/0.05 Torr, $[\alpha]_D^{20} = +326°$ ($c = 0.77$, EtOH). – UV. (EtOH): 224 (14,600). – CD. ($c = 6.56 \cdot 10^{-5}$ mol · l^{-1}, EtOH): $[\theta]_{236} = 58{,}800$, $[\theta]_{285} = 0$, $[\theta]_{318} = -3770$, $[\theta]_{380} = 0$. – IR. (liq.): 1735, 1675, 1620, 1250, 1040. – ^{1}H-NMR. (90 MHz): 0.87 and 0.97 (2 *s*, 6 H, 2 H_3C–C(1)); 1.59 (*m*, 3 H, H_3C–C(5)); 2.06 (*s*, 3 H, CH_3COO); 2.26 (*s*, 3 H, 3 H–C(10)); 4.88 (*d* × *d*, $J_{2,3} = 10$, $J_{2,3} = 6$, 1 H, H–C(2)); 5.42 (*m*, 1 H, H–C(4)); 6.06 (*d*, $J_{7,8} = 16$, 1 H, H–C(8)); 6.63 (*d* × *d*, $J_{7,8} = 16$, $J_{6,7} = 10$, 1 H, H–C(7)). – MS.: 250 (< 1, M^+), 235 (2), 190 (26), 175 (42), 157 (4), 147 (55), 137 (10), 121 (20), 105 (16), 93 (19), 72 (14), 55 (9), 43 (100).

2. Synthesis of compounds 7 and 15 from compound 8. – 2.1. *Synthesis of (1R,3S,6S)- and (1S,3S,6S)-2,2,6-trimethyl-7-oxobicyclo[4.4.0]dec-3-yl acetate* (**12** *and* **13**, *respectively*). Keto acetate **11** (1.04 g, 4.16 mmol, $[\alpha]_D^{20} = -6°$ ($c = 0.85$, $CHCl_3$), prepared from 60% optically pure **8** [8] in the same way as **6**) was dissolved in anh. ethanol and hydrogenated over 5% Rh/C (400 mg). The H_2 uptake ceased after 46 h. The solution was filtered and evaporated. The crude product, the ^{1}H-NMR. of which still indicated the presence of 25% of unreacted **11**, was dissolved in acetone (70 ml) and treated with 2.37 M CrO_3 in conc. H_2SO_4-solution/H_2O 23:77 (1.5 ml, 6 equiv.). The usual work-up left a mixture of **13** (54%), **12** (24%) and **11** (22%); GLC., *Carbowax 20 M*, **12** precedes **11** and **13**. Separation by chromatography on silica gel with hexane/ethyl acetate 9:1 yielded **13** (430 mg, 41%) as a solid and 570 mg of a 5:4 mixture of **12** and **11**. Sublimation of **13** at 75°/0.05 Torr gave a 97% pure sample (GLC., *Carbowax 20 M*); m.p. 81.5–84°, $[\alpha]_D^{20} = -5°$ ($c = 1.09$, $CHCl_3$). – IR. ($CHCl_3$): 1720, 1700, 1255. – ^{1}H-NMR. (60 MHz): 0.90, 0.98 and 1.18 (3 *s*, 9 H, 2 H_3C–C(2), H_3C–C(6)); 2.06 (*s*, 3 H, CH_3COO); 4.48 (*m*, 1 H, H–C(3)). – MS.: 252 (< 1, M^+), 210 (< 1). 192 (22), 177 (10), 159 (36), 149 (37), 121 (65), 82 (28), 43 (100).

The **12/11** mixture was recycled to give another 140 mg of **13** and 310 mg of **12/11** (88:12). A spectroscopic sample of **12** (oil) was isolated by prep. GLC. (*Carbowax 20 M*). – ^{1}H-NMR. (60 MHz): 0.91, 0.97 and 1.31 (3 *s*, 9 H, 2 H_3C–C(2), H_3C–C(6)); 2.04 (*s*, 3 H, CH_3COO); 4.57 (*t*, $J_{3,4} = 3$, 1 H, H–C(3)). – MS.: 252 (0, M^+), 192 (12), 177 (13), 159 (8), 149 (55), 121 (36), 82 (31), 43 (100).

2.2. *Synthesis of (–)-(1'S,3'S,6'S)-methyl 3-(3'-acetoxy-6'-methoxycarbonyl-2',2',6'-trimethylcyclohexyl)propionate* (**14**). The procedure was taken from [10] [11]. A mixture of **13** (504 mg, 2 mmol), ethanol (4 ml), 15% aq. NaOH-solution (0.8 ml) and freshly distilled 2-furaldehyde (0.2 ml) was stirred at RT. for 2 h. The crude product obtained after the usual work-up was acetylated with acetic anhydride/pyridine 1:2 (6 ml) at 70° for 3 h. Work-up and filtration through 35 g of silica gel with hexane/ethyl acetate 4:1 yielded 463 mg of furfurylidene derivative which was ozonolized in anh. dichloromethane (25 ml) at –78° until the solution turned blue. The mixture was purged with Ar and concentrated. Acetic acid (10 ml) and 35% H_2O_2-solution (2 ml) were added. After stirring at RT. overnight, most of the solvent was removed (RV.). The residue was taken up in ether and worked up in the usual manner. The crude product was esterified with an excess of ethereal diazomethane at RT. for 30 min. The resulting **14** was then purified by chromatography on 60 g of silica gel with hexane/ethyl acetate 9:1. Upon bulb-to-bulb distillation at 145° (bath)/0.005 Torr, 254 mg (38%) of semicrystalline **14** were obtained, $[\alpha]_D^{20} = -6°$ ($c = 1.15$, $CHCl_3$). – IR. ($CHCl_3$): 1720, 1255. – ^{1}H-NMR. (60 MHz): 0.93 (*s*, 6 H, 2 H_3C–C(2')); 1.22 (*s*, 3 H, H_3C–C(6')); 2.05 (*s*, 3 H, CH_3COO); 3.62 and 3.64 (2 *s*, 6 H, 2 CH_3OOC); 4.60 (*m*, 1 H, H–C(3')). – MS.: 328 (0, M^+), 209 (60), 168 (39), 135 (41), 121 (30), 43 (100), 41 (47).

2.3. *Synthesis of (+)-(1'R,3'S,6'S)-methyl 3-(3'-acetoxy-6'-methoxycarbonyl-2',2',6'-trimethylcyclohexyl)propionate* (**18**). As above **12** (176 mg, 0.7 mmol) was converted into 68 mg (29%) of **18**, $[\alpha]_D^{20} = +48°$ ($c = 0.83$, $CHCl_3$). – IR. ($CHCl_3$): 1720, 1255. – ^{1}H-NMR. (90 MHz): 0.78 and 0.90 (2 *s*, 6 H, 2 H_3C–C(2')); 1.23 (*s*, 3 H, H_3C–C(6')); 2.07 (*s*, 3 H, CH_3COO); 3.63 and 3.66 (2 *s*, 6 H,

2 CH_3OOC); 4.66 (*t*, $J_{3',4'}=3$, 1H, H–C(3')). – MS.: 328 (0, M^+), 209 (52), 168 (15), 135 (37), 121 (33), 43 (100), 41 (45).

2.4. *Synthesis of (+)-(1R,3S,6S)-2,2,6-trimethyl-7-oxobicyclo[4.3.0]non-3-yl acetate* (**7**). A procedure described in [10] was used. Potassium (70 mg, 1.8 mmol) was dissolved in 4 ml of anh. *t*-butyl alcohol. The excess of *t*-butyl alcohol was removed by repeated codistillation with anh. benzene. Ester **18** (45 mg, 0.14 mmol) and benzene (5 ml) were added. The mixture was heated at 80° for 4 h while the solvent was slowly distilled off. From time to time more benzene was added. Stirring was continued at RT. overnight. The mixture was added to ice-cold 10% aq. HCl-solution and extracted with ether. The crude keto ester obtained after solvent removal was hydrolyzed and decarboxylated by heating it in acetic acid (2 ml), conc. HCl-solution (1 ml) and water (0.2 ml) at reflux temp. for 1 h. The solvents were removed by azeotropic distillation with benzene. The residue was acetylated with acetic anhydride/pyridine 1:2 (0.9 ml) overnight. After work-up, 38 mg of **7** were obtained as an oil. Purification was achieved by prep. GLC. (5% *SOMB*), $[\alpha]_D^{20}=+24°$ ($c=0.78$, $CHCl_3$). – IR., ^{1}H-NMR. and MS.: identical with the ones of 7 obtained from **3**.

2.5. *Synthesis of (+)-(1S,3S,6S)-2,2,6-trimethyl-7-oxobicyclo[4.3.0]non-3-yl acetate* (**15**). As above **14** (150 mg, 0.46 mmol) was converted to 80 mg of semicrystalline **15**, $[\alpha]_D^{20}=+52°$ ($c=0.83$, $CHCl_3$). – IR. (liq.): 1735, 1240, 1020. – ^{1}H-NMR. (90 MHz): 0.96, 1.03 and 1.05 (3 *s*, 9 H, 2 H_3C–C(2), H_3C–C(6)); 2.10 (*s*, 3 H, CH_3COO); 4.57 (*d*×*d*, $J_{3,4ax}=10$, $J_{3,4eq}=5$, 1H, H–C(3')). – MS.: 238 (9, M^+), 178 (19), 163 (10), 148 (70), 134 (71), 119 (89), 105 (46), 91 (70), 69 (33), 55 (35), 43 (100).

3. Preparation of compound 14 from ursolic acid (16). The procedure was adopted from [13]. A solution of **17**[12]) (640 mg, 1.25 mmol, m.p. 151.5–152°, $[\alpha]_D^{20}=-89°$ ($c=0.86$, $CHCl_3$)) in anh. dichloromethane was ozonolized at –78° for 30 min. Water (9 ml) was added, and the dichloromethane was removed at reduced pressure. The aq. phase was brought to pH 7 with $NaHCO_3$-solution and treated with 2.5 ml of 35% H_2O_2-solution at 60° for 15 min. The mixture was extracted with ether. The aq. layer was acidified with conc. H_2SO_4-solution and extracted with ether. The usual work-up and treatment of the acidic part with an excess of ethereal diazomethane solution gave 128 mg (31%) of crude **14**. Chromatography on 20 g of silica gel with hexane/ethyl acetate 3:1 gave 61 mg of pure, oily ester **14**, $[\alpha]_D^{20}=-10°$ ($c=1.12$, $CHCl_3$). – IR., ^{1}H-NMR. and MS.: superimposable on those of **14** derived from **8**.

4. Synthesis of compound 33 from (–)-*trans*-verbenol (42). – 4.1. *Synthesis of (–)-(S)-2,2,4-trimethyl-3-cyclohexene-1-carbaldehyde* (**43**). (–)-*trans*-Verbenol ($[\alpha]_D^{20}=-101°$ (neat, $l=1$ dm); 95 g) was pyrolyzed by downward passage through a quartz tube (50×1.5 cm) filled with sintered quartz rings[13]) at 345° in a current of N_2 at a rate of 30 ml/min. The crude pyrolysate (90 g) was stirred at RT. with saturated $NaHSO_3$-solution (1 l) during 18 h, after which the mixture was acidified with 10% aq. H_2SO_4-solution. The aqueous layer was washed with ether (3 times 200 ml), cooled by the addition of ice, and made alkaline with cold dilute NaOH-solution. The product was immediately extracted 3 times with ether (delay led to epimerization of the product). The extracts were then immediately washed to neutrality and dried, the solvent was removed and the product distilled to give 20 g (21%) of **43** (pure by GLC.), b.p. 38°/0.7 Torr, $[\alpha]_D^{20}=-53°$ (neat, $l=1$ dm). – IR. (liq.): 2710, 1720. – ^{1}H-NMR. (60 MHz): 0.96 and 1.18 (2 *s*, 6 H, 2 H_3C–C(2)); 1.63 (br. *s*, 3 H, H_3C–C(4)); 5.07 (*m*, $w_{1/2}=4$, 1H, H–C(3)); 9.71 (*d*, $J=2$, 1H, CHO). – MS.: 152 (41, M^+), 137 (28), 121 (55), 109 (69), 107 (56), 96 (35), 81 (100), 69 (34), 67 (45), 55 (27), 43 (30), 41 (47).

4.2. *Synthesis of (+)-(1S,3R,4S)-3,4-epoxy-2,2,4-trimethylcyclohexyl formate* (**44**). *m*-Chloroperbenzoic acid (*Aldrich;* 86%, 51 g, 250 mmol) was slowly added in portions to a stirred solution of **43** (20 g, 132 mmol) in chloroform (200 ml) at 0°. The mixture was stirred at RT. for 9 days when GLC. showed reaction to be complete. The precipitate was filtered off, and the filtrate was washed with cold $NaHCO_3$-solution and water. After drying and solvent removal, distillation (bulb-to-bulb) of the residue at 100° (bath)/0.1 Torr gave **44** (pure by GLC., 8 g, 33%), $[\alpha]_D^{20}=+32°$ (neat, $l=1$ dm). – IR. (liq.): 1715. – ^{1}H-NMR. (60 MHz): 1.02 and 1.06 (2 *s*, 6 H, 2 H_3C–C(2)); 1.28 (*s*, 3 H, H_3C–C(4));

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[12]) Ursolic acid (**16**) was isolated from dried leaves of *Vinca minor* L. [13] [30] and converted to the triene **17** according to [12] [13].

[13]) For a description of the apparatus used see [31].

2.46 (*s*, 1H, H–C(3)); 4.65 (*m*, 1H, H–C(1)); 7.95 (*s*, 1H, HCOO). – MS.: 184 (< 1, M^+), 138 (13), 123 (17), 109 (10), 95 (43), 83 (23), 69 (27), 55 (23), 43 (100), 41 (32).

4.3. *Synthesis of (+)-(1S,5S)-5-hydroxy-4,6,6-trimethyl-3-cyclohexenyl formate* (**45**). To a solution of **44** (5 g) in dioxane (dried over molecular sieves 4 Å, 100 g) was added FILTROL® (1 g, grade 13, dried at 130°) with stirring at 10°, after which the mixture was allowed slowly to reach RT. After 1 h the mixture was filtered and the filtrate evaporated (RV.). The residue (5.1 g) was used as such for the next step; a sample purified by bulb-to-bulb distillation at 110° (bath)/0.1 Torr showed $[\alpha]_D^{20} = +63°$ (neat, $l = 1$ dm). – IR. (liq.): 3400, 1720. – ^{1}H-NMR. (60 MHz): 0.90 and 0.98 (2 *s*, 6H, $2\,H_3C$–C(6)); 1.78 (br. *s*, 3H, H_3C–C(4)); 2.8 (*s*, 1H, HO, disappears on adding D_2O); 3.47 (*s*, 1H, H–C(5)); 4.99 (*m*, 1H, H–C(1)); 5.2 (*m*, 1H, H–C(3)); 8.01 (*s*, 1H, HCOO).

4.4. *Synthesis of (1S,3S)-2,2,4-trimethyl-4-cyclohexene-1,3-diol* (**46**). Hydroxy formate **45** (0.5 g) was hydrolyzed by heating under reflux in ethanolic KOH-solution for 1 h, after which water was added and the product isolated by several extractions with ether. The extracts were washed with sat. NaCl-solution, the solvent was removed (RV.), and the residue distilled (bulb-to-bulb) at 120° (bath)/0.1 Torr to give **46** (0.35 g, 70%). – IR. (CCl_4): at 3.8% concentration sharp band at 3700 and broad band at 3450 cm^{-1}; the latter disappears at 0.095% concentration while the former remains practically unchanged. – ^{1}H-NMR. (60 MHz): 0.91 and 1.07 (2 *s*, 6H, $2\,H_3C$–C(2)); 1.75 (br. *s*, 3H, H_3C–C(4)); *ca.* 3.6 (*m*, 2H, H–C(1), H–C(3)); 5.25 (*m*, 1H, H–C(5)).

4.5. *Synthesis of (+)-(1S,3S)-2,2-dimethyl-4-methylidenecyclohexane-1,3-diol* (**47**). Butyllithium in hexane (15%, 100 ml, 164 mmol) was added dropwise with stirring under Ar at 10–20° to a solution of diethylamine (12 g, 164 mmol) in anh. ether (10 ml), after which a solution of **44** (5 g, 27 mmol) in anh. ether (50 ml) was added at the same temp. The mixture was stirred at RT. for 18 h and heated under reflux for 5 h [32]. It was then poured on ice and the organic layer washed with sat. NaCl-solution. The usual work-up followed by bulb-to-bulb distillation at 120° (bath)/0.1 Torr gave 3.6 g (85%) of **47** (pure by GLC.), $[\alpha]_D^{20} = +7.6°$ ($c = 7.5$, $CHCl_3$). – IR. (CCl_4): broad band at 3480 cm^{-1} which disappears on dilution while the sharp band at 3650 cm^{-1} remains practically unchanged (*cf.* **46**). – ^{1}H-NMR. (60 MHz): 0.90 (*s*, 6H, $2\,H_3C$–C(2)); 3.69 (*d*×*d*, $J_{1,6ax} = 7$, $J_{1,6eq} = 4$, 1H, H–C(1)); 3.9 (br. *s*, 1H, H–C(3)); 4.79 (br. *s*, 2H, H_2C=C(4)). – MS.: 156 (1, M^+), 138 (27), 123 (79), 109 (17), 95 (41), 83 (26), 71 (76), 69 (52), 55 (41), 43 (100), 41 (71).

4.6. *Synthesis of (+)-4,6,6-trimethyl-5-oxo-3-cyclohexenyl formate* (**48**). A solution of chromium trioxide (5 g) in water (5 ml) was slowly added to pyridine (50 ml). To this solution **45** (5 g) was added in one portion at 20°. The mixture was stirred overnight, diluted with ether (200 ml) and washed with cold dilute aq. H_2SO_4-solution. The usual work-up followed by bulb-to-bulb distillation gave 4.9 g (98%) of **48**, b.p. 120° (bath)/0.1 Torr, pure by GLC., $[\alpha]_D^{20} = +48°$ (neat, $l = 1$ dm). – IR. (liq.): 1710, 1650. – ^{1}H-NMR. (60 MHz): 1.07 and 1.13 (2 *s*, 6H, $2\,H_3C$–C(6)); 1.75 (*s* with long range coupling, 3H, H_3C–C(4)); 2.6 (*m*, 2H, 2H–C(2)); 5.10 (*d*×*d*, $J_{1,2} = 6$, $J'_{1,2} = 5$, 1H, H–C(1)); 6.48 (*m*, 1H, H–C(3)); 8.20 (*s*, 1H, HCOO). – MS.: 182 (< 1, M^+), 136 (31), 93 (10), 82 (100), 67 (5), 54 (23), 43 (16), 41 (18), 39 (15).

4.7. *Synthesis of (3S)-3-hydroxy-2,2,6-trimethylcyclohexanone* (**49**; *C(6)-epimeric mixture*). Keto ester **48** (27.1 g) was hydrolyzed by heating under reflux in methanolic NaOH-solution for 1 h, after which water was added and the product isolated by several extractions with ether. The crude product left after solvent removal (23 g) was hydrogenated in ethanol over Pd/C (1 g) and in the presence of KOH (2 g) until H_2 uptake ceased. Filtration, solvent removal from the filtrate (RV.), isolation of the product with ether and distillation gave 22 g (95%) of **49**, b.p. 76–80°/0.4 Torr, $[\alpha]_D^{20} = +32°$ (neat, $l = 1$ dm). – IR. (liq.): 3450, 1700. – ^{1}H-NMR. (60 MHz): 1.00 and 1.02 (2 *d*, $J = 6$, 3H, H_3C–C(6)); 1.13 and 1.16 (2 *s*, 6H, $2\,H_3C$–C(2)); 2.7 (*m*, 1H, H–C(6)); 3.54 and 3.94 (2 *m*, $w_{1/2} = 8$, $w'_{1/2} = 3$, 1H, H–C(3)). – MS.: 156 (24, M^+), 138 (7), 125 (2), 98 (26), 83 (100), 67 (51), 55 (50), 43 (62), 41 (62).

4.8. *Synthesis of (3S)-1-(3'-hydroxy-1'-butynyl)-2,2,6-trimethylcyclohexane-1,3-diol* (**50**)[5]). The procedures for this and subsequent steps were adopted from [27]. A solution of ethylmagnesium bromide was prepared in the usual manner from ethyl bromide (8.8 g, 81 mmol) and magnesium (2 g, 82 mmol) in ether (20 ml) under Ar, after which the ether was distilled off while adding anh. benzene (30 ml). A solution of 3-butyn-2-ol (2.8 g, 40 mmol) in anh. benzene (40 ml) was added and the mixture

heated under reflux for 1 h. Then **49** (3.2 g, 20.5 mmol) in anh. benzene (10 ml) was added at 20°. The whole was again heated under reflux for 4 h. After cooling, the mixture was hydrolyzed with saturated aq. NH_4Cl-solution, filtered, and the filtrate worked up in the usual manner. Bulb-to-bulb distillation at 150° (bath)/0.1 Torr gave 3.4 g (73%) of **50**[5]), $[\alpha]_D^{20} = +8.4°$ ($c = 10.6$, $CHCl_3$). – ^{1}H-NMR. (60 MHz): 0.94 and 1.12 (2 *d*, $J = 5.5$, 3 H, $H_3C-C(6)$); 1.04 and 1.24 (2 *s*, 6 H, 2 $H_3C-C(2)$); 1.36 (*d*, $J_{3',4'} = 6.5$, 3 H, 3 H–C(4′)); 3.6 (*m*, 1 H, H–C(1)); 4.47 (*qa*, $J_{3',4'} = 6.5$, 1 H, H–C(3′)).

4.9. *Synthesis of (1S)-3-(3′-acetoxy-1′-butynyl)-3-hydroxy-2,2,4-trimethylcyclohexyl acetate* (**51**)[6]). Triol **50** (3.4 g) was dissolved in acetic anhydride/pyridine 1:4 (25 g) and left at RT. for 4 h. The whole was poured on ice, and the product was isolated with ether. The residue left after solvent removal (RV.) was chromatographed on silica gel (deactivated with 18% water, 100 g) with petroleum ether/ether 7:3 giving 1.3 g (27%) of **51**[6]), $[\alpha]_D^{20} = +10.7°$ ($c = 10.7$, $CHCl_3$). – IR. (liq.): 3500, 1740. – ^{1}H-NMR. (60 MHz): 0.87 and 0.95 (2 *s*, 6 H, 2 $H_3C-C(2)$); 0.97 (*d*, $J = 6.5$, 3 H, $H_3C-C(4)$); 1.48 (*d*, $J_{3',4'} = 6.5$, 3 H, 3 H–C(4′)); 1.99 and 2.04 (2 *s*, 6 H, 2 CH_3COO); 4.77 (*m*, 1 H, H–C(1)); 5.53 (*qa*, $J_{3',4'} = 6.5$, 1 H, H–C(3′)). – MS.: 310 (0, M^+), 91 (41), 71 (40), 57 (100), 43 (69), 29 (25).

4.10. *Synthesis of (−)-(1S)-3-(3′-acetoxy-1′-butynyl)-2,2,4-trimethyl-3-cyclohexenyl acetate* (**52**; *C(3′)-epimeric mixture*). To a solution of **51** (300 mg) in pyridine (10 ml) was added phosphoryl chloride (1.1 g), and the mixture was stirred under Ar at 85° for 24 h. Then it was cooled, poured on ice, and the product extracted exhaustively with ether. The extracts were washed to neutrality with aq. $NaHCO_3$- and sat. NaCl-solution. After solvent removal the residue was chromatographed on alumina (100 g, act. IV) with hexane/ether 5:1 giving 120 mg (43%) of **52**, $[\alpha]_D^{20} = -10°$ ($c = 10.4$, $CHCl_3$). – IR. ($CHCl_3$): 1740. – ^{1}H-NMR. (60 MHz): 1.05 and 1.08 (2 *s*, 6 H, 2 $H_3C-C(2)$); 1.48 (*d*, $J_{3',4'} = 6.5$, 3 H, 3 H–C(4′)); 1.83 (*s*, 3 H, $H_3C-C(4)$); 2.02 (*s*, 6 H, 2 CH_3COO); 4.7 (*m*, 1 H, H–C(1)); 5.47 (*qa*, $J_{3',4'} = 6.5$, 1 H, H–C(3)).

4.11. *Synthesis of (−)-(2S)-2-hydroxy-β-ionol (=(1S,1′E)-3-(3′-hydroxy-1′-butenyl)-2,2,4-trimethyl-3-cyclohexen-1-ol;* **53**; *C(3′)-epimeric mixture*). Diacetate **52** (100 mg) in anh. THF (10 ml) was reduced with $LiAlH_4$ (300 mg) at reflux temp. for 18 h. After cooling aq. solution of sodium tartrate (20%, 10 ml) was added, and the mixture was extracted with ether. After the usual work-up the product was purified by chromatography on alumina (100 g, act. IV) with hexane/ether 4:1 to give 60 mg (84%) of **53**, $[\alpha]_D^{20} = -9°$ ($c = 10.7$, $CHCl_3$). – ^{1}H-NMR. (60 MHz): 0.95 and 1.02 (2 *s*, 6 H, 2 $H_3C-C(2)$); 1.27 (*d*, $J_{3',4'} = 6$, 3 H, 3 H–C(4′)); 1.66 (br. *s*, 3 H, $H_3C-C(4)$); 3.48 (*m*, 1 H, H–C(1)); 4.37 (*qi*, $J_{2',3'} = J_{3',4'} = 6$, 1 H, H–C(3′)); 5.40 (*d*×*d*, $J_{1',2'} = 16$, $J_{2',3'} = 6$, 1 H, H–C(2′)); 5.96 (*d*, $J_{1',2'} = 16$, 1 H, H–C(1′)).

4.12. *Synthesis of (−)-(S)-2-hydroxy-β-ionone* (**33**). A solution of **53** (30 mg) was stirred in anh. acetone (10 ml) with manganese dioxide (*Merck;* 1 g) at RT. for 18 h. Filtration, evaporation of the filtrate (RV.) and chromatography of the residue on alumina (70 g, act. IV) with hexane/ether 1:1 gave 12 mg (40%) of **33**, $[\alpha]_D^{20} = -8°$ ($c = 11$, EtOH). – IR., ^{1}H-NMR. and MS.: identical with those of the sample prepared according to 1.14.

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