Tetrahedron Vol. 43, No. 22, pp. 5287 to 5298, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

TERPENES AND TERPENE DERIVATIVES - 22.[1] SYNTHESIS OF RAC. ISOCANAMBRIN AND 6-EPI-ISOCORDILIN

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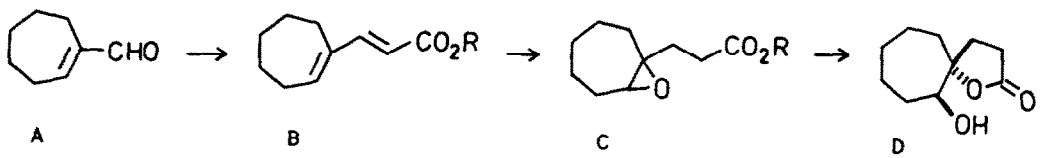
(*Received in Germany* 11 *August* 1987)

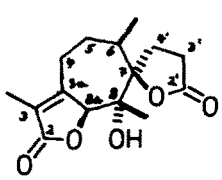
ABSTRACT - Isocanambrin (1) and 6-epi-isocordilin (21) were synthesized by twofold application of a reaction sequence starting from an α,β-unsaturated carbonyl compound via Wittig-Horner reaction, selective hydrogenation, epoxidation, and solvolysis to give a hydroxy- γ-lactone. Thus, aldehyde 4 was converted (→ 5, → 8, → 9) to the key compounds 10a and b. From 10a (→ 14a, → 15a, → 16a, → 18a, → 19a) the (Z)-ester 20a was prepared which afforded the title compound 1 by hydrolysis. An analogous sequence leads from 10b to 21.

Some years ago we described a reaction sequence starting from cycloalkene carbaldehydes (e.g. A) leading to a trans-hydroxy spiro-γ-lactone (D) via Wittig-Horner reaction (→ B), selective epoxidation and hydrogenation, or vice versa, (→ C) and acidic hydrolysis[2]. Obviously, the hydrolysis occurs in a S_N2 type because in general we found isomers with trans geometry of the oxygen functions.

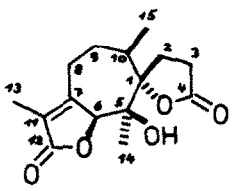


A B C D

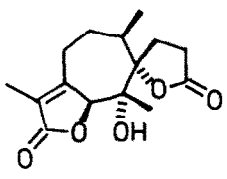
To use this sequence for natural product synthesis we chose as target molecules the pseudoguaianolides isocanambrin[3] (1), isocordilin[4] (2), and isopsilostachyin[5] (3) which are easily formed by catalytic isomerization from canambrin, cordilin, and psilostachyin, physiologically and chemotaxonomically interesting constituents of Ambrosia species (structures 1-3, but Δ11,13 instead of Δ7,11). Both the relative and absolute configurations of 1-3 were assigned[4] by correlation with bromoambrosin which configuration was established by X-ray analysis[6].



1 Isocanambrin



2 Isocordilin

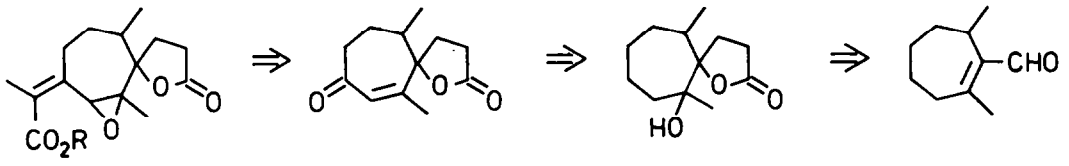


3 Isopsilostachyin

IUPAC (1) and sesquiterpene (2) nomenclature, the latter one is used throughout the text, the former one in the experimental part.

The synthesis of 1-3 is particularly challenging since these compounds possess the structural element of hydroxysubstituted γ-lactones twice. According to the retrosynthetic scheme the key compound is hydroxylactone G which was obtained in low yield together with the respective δ-lactone in an investigation of partial structures of terpenic lactones[7].

We focussed our attention on the synthesis of G via the same sequence we had selected for D. Dehydration of G and subsequent oxidation should give F, a convenient starting material for epoxidation, Wittig-Horner reaction (→ E), and hydrolysis to provide 1-3.



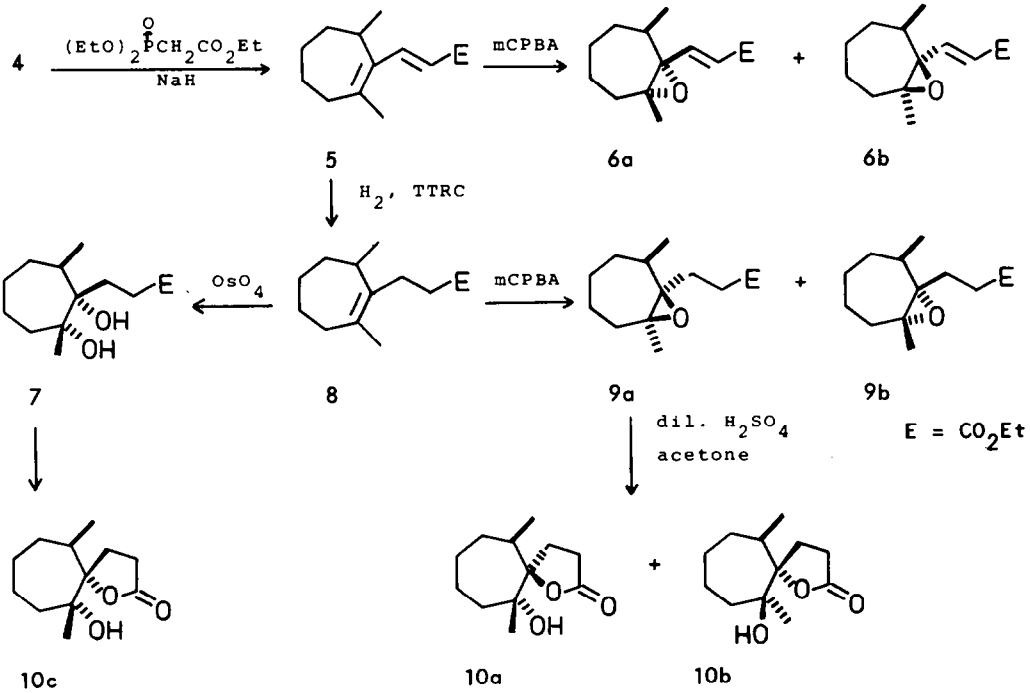
E F G 4

RESULTS AND DISCUSSION

The formation of the spirolactone ring started with the α,β-unsaturated aldehyde 4, readily available by Nozaki's method[8] from 2,7-dimethylcycloheptanone[9]. Olefination of 4 with triethyl phosphonoacetate (NaH/dioxane) gives the diene ester 5. Epoxidation of 5 with mCPBA occurs regio but not stereoselectively (→ 6a,b, ≈1:1). Therefore, the α,β-double bond of 5 was selectively hydrogenated with the homogeneous catalyst TTRC to give ester 8.

Epoxidation of 8 with mCPBA leads in quantitative yield stereoselectively[10] to 9a with trans methyl groups which could be assigned unambiguously by NOED spectra. Both methyl groups of 8 are quasi equatorial in the most favored conformation, and the peracid attacks anti to the quasi axial 10-H.

Hydrolysis of 9a with diluted sulfuric acid in acetone[2] yields almost quantitatively a mixture of the hydroxylactones 10a and b (1:1) separable by CC on alumina. The γ-lactone moiety is established by δ_C 178.1 ppm for the carbonyl group and the relative configuration at C-1, -5, and -10 was again proven by NOED spectra. This result is only in agreement with ring opening reactions of the protonated epoxide 9a to give two different trans diols followed by ring closure to 10a and b in equal amounts.



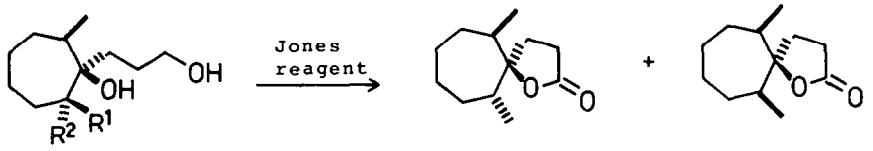
5 6a 6b

7 8 9a 9b

10c 10a 10b

Contrary to Dutta's report[7] we never obtained δ-lactones. This, and other confusions in ref.[7] prompted us to repeat this work in part in order to obtain clear assignments by modern spectroscopic methods.

First, the isomeric mixture of diol 11a,b[7] (the symmetric 11b can be obtained pure by CC) gives by Jones oxidation directly the separable mixture of lactones 12a and b (same ratio 2:1 as 11). The magnetically equivalent methyl groups of 12b give only one ^{1}H NMR signal (δ 0.98; ref.[7] 1.0, 0.904), and the ^{13}C NMR spectrum of 12b shows only eight signals, thus confirming the cis configuration of 12b.



11a R^1: H, R^2: Me 12a 12b

11b R^1: Me, R^2: H

Second, osmium tetroxide oxidation of 8 affords via diol 7 the cis-hydroxy lactone 10c. The configuration of 10c is proven by ^{1}H NOED and ^{13}C DEPT spectra.

Third, treatment of 9a with aqueous sodium hydroxide followed by hydrochloric acid gives a mixture (2:1) of 10a and b with traces (<5%) of 10c (arising perhaps from the small amount of 9b, see[10]).

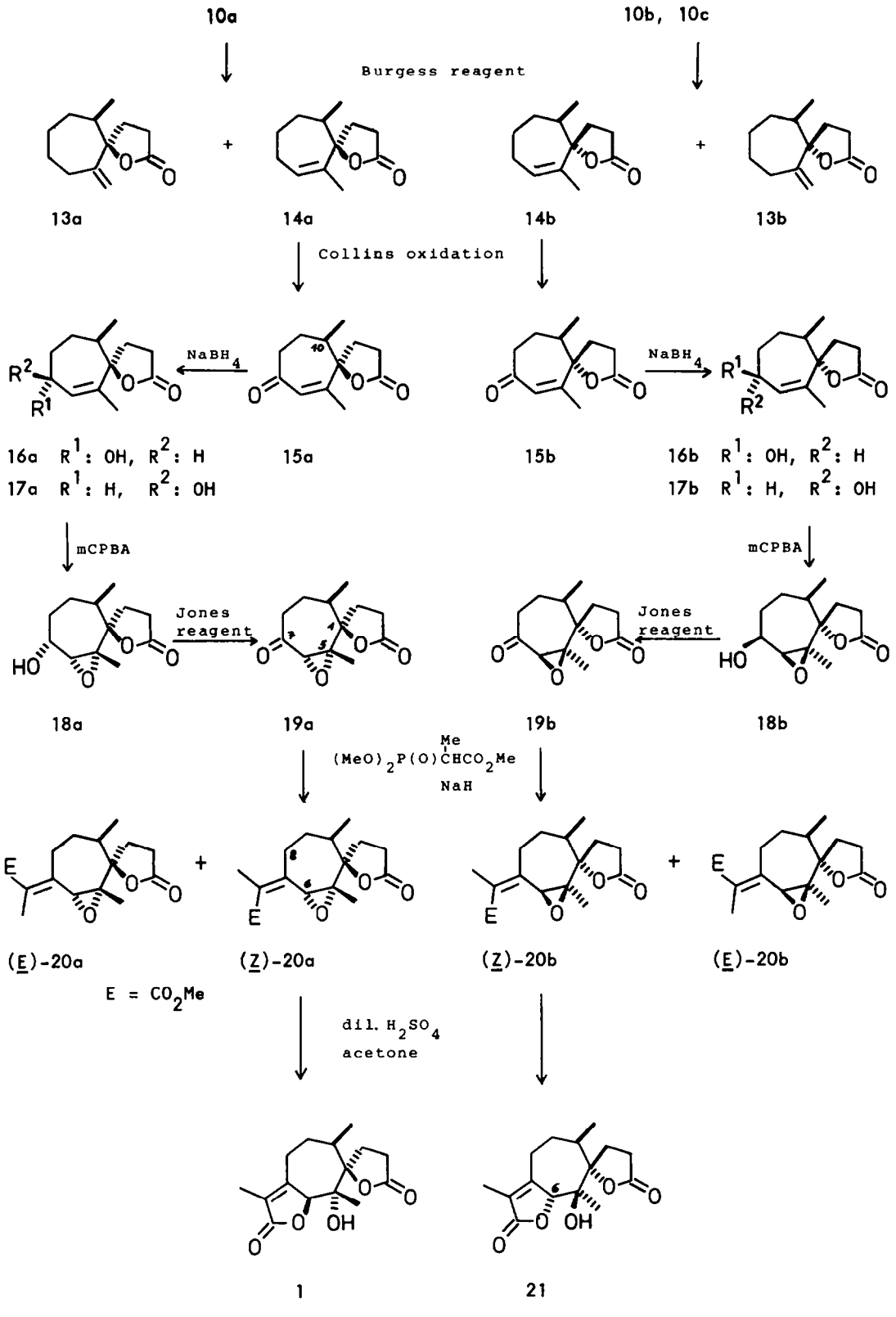
Thus, the geometry of the spirolactones 10 was well established, and due to the excellent yields we were able to prepare 10a (→ isocanambrin, 1) and 10b (→ isocordilin, isopsilostachyin, 2, 3) in relatively large amounts.

Dehydration of seven-membered ring compounds is often complicated because ring contraction can readily occur via cationic rearrangement. If this reaction of 10a is carried out with $KHSO_4$, oxalic acid, or p-toluene sulfonic acid, mixtures are formed. $POCl_3$/pyridine affords mainly the exo-isomer 13a, but Burgess reagent[11] gives a 13a/14a mixture (1:2) in 90% yield. From 10b the 13b/14b ratio is even better (1:6). Dehydration of 10c also yields 13b/14b (≈1:1) thus giving a further confirmation of the right configuration assignment in lactones 10. - However, the 13/14 isomers are difficult to separate and therefore we used these mixtures for the next step.

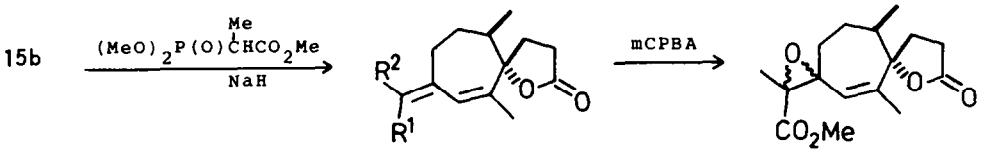
The allyl oxidation 14 → 15 was much more difficult than expected, since some recommended reagents failed. SeO_2 in ethanol[12] gives allyl ethylethers, but in dioxane[13] allylalcohols and the α,β-unsaturated aldehyde. Na_2CrO_4 in AcOH/Ac_2O[14] oxidizes the methylene group with addition of AcOH. PDC[15] and PCC[16] did not react at all. However, Collins reagent was successful providing the best yield by preparation of the reagent in situ highly diluted[17]. Thus, 14a reacted selectively to 15a, 14b to 15b, and both unsaturated ketones are readily separable from the unchanged 13a and b.

Going on with 15a or b the next two steps for fusion of the second lactone ring - epoxidation and Wittig-Horner reaction - should be exchangeable[2]. First, we tried to epoxidize 15a and b assuming that the α-epoxides will be formed by steric direction of the 10-methyl group, important for the correct configuration at C-5. Despite numerous variations we were not able to epoxidize 15a and b. With H_2O_2/NaOH the lactone ring was cleaved, although α,β-unsaturated ketones have been oxidized even in presence of γ-lactones[18,19]. Reaction with the highly efficient reagents tBuOOH (aqueous[20] or dry[21]) or cumylhydroperoxide and Triton B[22] failed. Obviously, the double bond is extremely hindered.

With mCPBA we obtained a dilactone by Baeyer-Villiger oxidation, and experiments for acetalization of the keto group of 15 remained unsuccessful.


10a
10b, 10c
Burgess reagent
13a
14a
14b
13b
Collins oxidation
NaBH4
NaBH4
16a R1: OH, R2: H
17a R1: H, R2: OH
15a
15b
16b R1: OH, R2: H
17b R1: H, R2: OH
mCPBA
mCPBA
Jones reagent
Jones reagent
18a
19a
19b
18b
(MeO)2P(O)CHCO2Me
Me
NaH
(E)-20a
(Z)-20a
(Z)-20b
(E)-20b
E = CO2Me
dil. H2SO4
acetone
1
21

Now, we turned to the Wittig-Horner reaction of 15 facing the next problem of selective γ,δ-epoxidation. Reaction of 15b with trimethyl phosphonopropionate (NaH/dioxane) gives the (E,Z)-mixture (1:4) of diene ester 22. Pure (Z)-22 could be isolated by fractional crystallization. The structural assignment is based on the δ_H values of the olefinic proton with 6.24 (Z) and 5.30 (E) ppm.
Epoxidation of (Z)-22 with mCPBA leads surprisingly only to the α,β-epoxide 23 easily detectable by NMR spectra. Here the more electron deficient double bond is favored for steric reasons, though the γ,δ-double bond of some α,β,γ,δ-dienones was selectively epoxidized even if lower alkyl substituted[23,24].



(Z)-22 R^1: CO_2Me, R^2: Me 23
(E)-22 R^1: Me, R^2: CO_2Me

Now, we turned again to the epoxidation for the first step, but including the variation that the ketones 15a and b were reduced with $NaBH_4$ to give the allyl alcohols 16a and b together with small amounts of the epimers 17a (20%) and 17b (10%). The Dreiding model shows that the preferred conformations of 15a and b with two quasi equatorial methyl groups lead to hydride approach cis to the ether oxygen of the spiro lactone. - Crude 16a and b were epoxidized with mCPBA stereoselectively cis to the hydroxyl group[25] to give 18a and b. Minor products are the epoxides from 17a,b with epimeric C-5, -6, and -7. - Sharpless epoxidation[26] of 16 with $tBuOOH/Mo(CO)_6$ gave a mixture of oxidation products in accordance with earlier results with sterically fixed allyl alcohols[27,28]. - Jones oxidation of 18a and b affords the epoxyketones 19a and b easily purified by recrystallization.
The stereoselectivity of both $NaBH_4$ reduction and epoxidation allows the determination of configuration at C-5 relatively to C-1 and C-10, even after removal of the chiral centre at C-7. In this sense 19a belongs to isocanambrin (1), 19b to isocordilin (2).
Reaction of 19a and b with trimethyl phosphonopropionate (NaH/dioxane) leads to the (Z)-esters 20a and b as major products (6:1 to 8:1). This unexpectedly high Z/E-ratio can be explained by an electronic interaction of the oxirane with the ester group. CC gives pure (Z)-20a and (Z)-20b. The assignment can be made by the downfield shift of 6-H (Z-isomer) and 8-H (E-isomer), located close to the ester group. (Z)-20a and -b were hydrolyzed with diluted sulfuric acid in acetone to give one hydroxy dilactone each. In accordance with previous results for hydrolysis of α,β-unsaturated γ,δ-epoxy esters of similar type[29], backside attack of the ester group to the protonated epoxide leads to a hydroxy substituted γ-lactone with trans oxygen functions. Thus, the configuration is retained at the δ-C-atom (C-5), inverted at the γ-C-atom (C-6). Therefore, the hydrolysis of (Z)-20a gives rac. isocanambrin (1), identical in the ^1H NMR data with those published for the natural product[3]. NOED spectra confirm the relative configuration at C-1, -5, and -6. Consequently, the same considerations lead to the configuration of the hydrolysis product of (Z)-20b. Here the hydroxyl group at C-5 should be in the β-, the O-function at C-6 in the α-position. Also this assignment could be evidenced by NOED spectra. Hence, this hydroxylactone is neither isocordilin (2) nor isopsilostachyin (3) but the hitherto unknown 6-epi-isocordilin (21).

EXPERIMENTAL

^{1}H NMR: in $CDCl_3$, Bruker WM 400 (internal TMS). - ^{13}C NMR: in $CDCl_3$, Bruker WH 270 with DEPT program, or Varian CFT 20, off resonance. - IR: in CCl_4, Perkin-Elmer 257. - MS: Varian-MAT 711, 70 eV. - C,H-Analyses: Hewlett Packard C,H,N-Analyzer. - Melting points: Büchi SMP-20. - Kugelrohr distillation: b.p. means temp. of the air bath. - Column chromatography (CC): Aluminium oxide, neutral, desactivated with 3% water. - Flash chromatography (FC):ICN Biomedicals silica gel 32-63. - Acetone, benzene, methanol, >99.5%, were purchased from Merck. - Dioxane and ether were distilled from NaH; CH_2Cl_2 from $CaCl_2$; pyridine from KOH. - Petroleum ether (PE) had b.p. 30-60°C. - Hexamethylphosphoric triamide (HMPT) had b.p. 112-114°C/12 Torr. - All solvents were stored over molecular sieves. - NaH: 80% dispersion in mineral oil. - 3-Chloroperoxybenzoic acid (mCPBA) contains 15% 3-chlorobenzoic acid. - Jones reagent: 26.7 g of CrO_3, 23 ml of concd. H_2SO_4 filled up to 100 ml with water. - All reactions were run in flamed vessels under an atmosphere of nitrogen except those in which water was present. - Usual work-up: Reaction products were isolated by the addition of water and extracted with the specified solvent. The combined extracts were washed to neutrality and then with satd. brine and dried over $MgSO_4$. The solvent was removed (after filtration) in vacuo on a rotary evaporator. - The ratio of isomers was determined by integration of typical signals in the ^{1}H NMR spectrum. - Numbering in the experimental part is according to IUPAC names.

2,7-Dimethyl-1-cycloheptene-1-carbaldehyde (4):

360 ml of a THP/PE/ether mixture (4:1:1) and 25.5 g (0.30 mol) of CH_2Cl_2 were cooled to -110°C and 190 ml (0.30 mol) of BuLi (15%) in hexane were added dropwise. After stirring for 30 min, 35.0 g (0.25 mol) of freshly distilled 2,7-dimethylcycloheptanone[9] were added at -110°C within 20 min. The solution was stirred for 1 h at -110°C and 1.5 h at -80°C, then allowed to come to room temp. and refluxed for 2 h. The solvents were removed at room temp., then 375 ml of HMPT, 61 g of $CaCO_3$, and 56 g of anhydrous $LiClO_4$ were added. The mixture was heated to 130°C for 18 h, cooled to 0°C, poured into 2 l of ice water, and extracted with PE. Work-up gave 25.8 g (68%) of 4, b.p. 110°C/13 Torr. - IR: 1670, 1625 cm^{-1} (C=C-CO). - ^{1}H NMR: δ = 1.04 (d, J = 7 Hz, 7-Me), 2.17 (s, 2-Me), 2.13, 2.55 (AB, J = 15, A-part dd, J = 7, 2, B-part dd, J = 12, 2 Hz, 3-H_2), 3.34 (mc, 7-H), 10.04 (s, CHO). - ^{13}C NMR: δ = 17.0, 20.7 (2 q, 2-, 7-Me), 24.8, 25.9, 31.8, 37.4 (4 t, C-3-6), 29.2 (d, C-7), 142.6 (s, C-1), 160.0 (s, C-2), 191.2 (d, CHO). - MS: m/z (%): 152 (M^+, 72), 137 (35), 123 (70), 109 (35), 95 (55), 91 (35), 81 (100), 79 (45), 67 (82), 55 (72), 53 (35). - $C_{10}H_{16}O$ calcd. C 78.90, H 10.59, found C 78.74, H 10.45.

Ethyl (E)-3-(2,7-dimethyl-1-cyclohepten-1-yl)-2-propenoate (5):

To a slurry of 4.5 g (0.15 mol) of NaH in 200 ml of dioxane a solution of 33.6 g (0.15 mol) of triethyl phosphonoacetate in 100 ml of dioxane was added dropwise. After stirring for 45 min a solution of 15.2 g (0.10 mol) of 4 in 150 ml of dioxane was added dropwise. After stirring for 1 d and solvent removal the mixture was poured into 800 ml of ice water, and extracted with ether. After work-up the crude 5 was passed through a short column of silica gel (PE/ether 9:1). Distillation afforded 20.7 g (93%) of 5, b.p. 75°C/0.05 Torr. - IR: 1710 (COOR), 1615 cm^{-1} (C=C). - ^{1}H NMR: δ = 1.11 (d, J = 7 Hz, 7-Me), 1.29 (t), 4.20 (q, J = 7 Hz, (COOEt), 1.95 (s, 2-Me), 2.10, 2.50 (AB, J = 16, A-part dd, J = 6, 3, B-part dd, J = 12, 3 Hz, 3-H_2), 2.85 (mc, 7-H), 5.83 (d), 7.76 (d, J = 16 Hz, CH=CH). - ^{13}C NMR: δ = 17.5, 23.1 (2 q, 2-, 7-Me), 24.6, 25.8, 32.2, 35.8 (4 t, C-3-6), 33.8 (d, C-7), 136.3 (s, C-1), 146.1 (s, C-2); CH=CH-COOEt: 144.7 (d), 115.2 (d), 168.1 (s), 60.0 (t), 14.4 (q). - MS: m/z (%): 222 (M^+, 48), 207 (40), 148 (80), 107 (66), 93 (96), 91 (100), 79 (75), 55 (90). - $C_{14}H_{22}O$ calcd. C 75.63, H 9.97, found C 75.45, H 9.98.

Ethyl (E)-r-3-(c-2,c-7)- (6a) and (E)-r-3-(t-2,c-7)-dimethyl-8-oxabicyclo[5.1.0]oct-1-yl)-2-propenoate (6b):

A solution of 9.3 g (53 mmol) of mCPBA in 150 ml of CH_2Cl_2 was added dropwise at 0°C to a stirred solution of 11.1 g (50 mmol) of 5 in 80 ml of CH_2Cl_2. After stirring for 4 h at 0°C work-up yielded 9.9 g (83%) of 6a/b (1.2:1), b.p. 75°C/0.02 Torr. - IR: 1720 (COOR), 1660 cm^{-1} (C=C). - ^{1}H NMR: δ = 0.96 (a)/0.98 (b, d, J = 7 Hz, 2-Me), 1.17 (s, 7-Me), 1.28/1.29 (t), 4.19/4.20 (q, J = 7 Hz, COOEt), 5.89/(b)/5.95 (a), 7.02 (b)/7.09 (a, d, J = 15.5 Hz, CH=CH). - ^{13}C NMR: δ = 17.9, 19.0, 19.3, 21.7 (4 q, 2-, 7-Me), 23.8, 24.9, 26.2, 29.7, 31.8, 33.5, 35.1, 36.2 (8 t, C-3-6), 35.6, 38.7 (2 d, C-7), 67.6, 67.8, 69.1, 70.3 (4 s, C-1, -2); 121.1, 123.1, 143.6, 148.7 (4 d), 166.3, 166.5 (2 s), 60.4 (t), 14.3 (q); CH=CH-COOEt. - MS: m/z (%): 238 (M^+, 5), 223 (3), 165 (45), 139 (70), 43 (100). - $C_{14}H_{22}O_3$ calcd. C 70.56, H 9.30, found C 70.29, H 9.22.

Ethyl 3-(2,7-dimethyl-1-cyclohepten-1-yl)-propionate (8):

8.9 g (40 mmol) of 5 were hydrogenated for 3 d with 0.40 g of $(PH_3P)_3RhCl$ (TTRC) in 80 ml of benzene. The solvent was removed. Distillation yielded 8.9 g (99%) of 8, b.p. 70°C/0.03 Torr. - IR: 1740 cm^{-1} (COOR). - ^{1}H NMR: δ = 1.07 (d, J = 7 Hz, 7-Me), 1.66 (s, 2-Me), 2.02, 2.19 (AB, J = 14, A-part dd, J = 8, 2.5, B-part dd, J = 10, 2.5 Hz, 3-H_2), 2.40 (mc, 7-H); 2.30 (t, J = 8 Hz), 1.25 (t), 4.11 (q, J = 7 Hz); CH_2-COOEt. - ^{13}C NMR: δ = 17.9, 22.1 (2 q, 2-, 7-Me), 23.8, 26.2, 31.8, 35.1 (4 t, C-3-6), 38.1 (d, C-7), 132.2, 136.8 (2 s, C-1, -2); 34.0, 34.6 (2 t), 173.4 (s), 60.2 (t), 14.3 (q); CH_2CH_2COOEt. - MS: m/z (%): 224 (M^+, 34), 209 (7), 136 (32), 123 (100), 109 (55), 95 (73), 81 (97), 67 (61), 55 (68). - $C_{14}H_{24}O_2$ calcd. C 74.95, H 10.78, found C 74.70, H 10.61.

Ethyl r-3-(t-2,c-7-dimethyl-8-oxabicyclo[5.1.0]oct-1-yl)-propionate (9a)[10]:

7.9 g (35 mmol) of 8 were treated with 7.0 g (40 mmol) of mCPBA as described for 5. Yield: 8.35 g (99%) of 9a[10], b.p. 80°C/0.05 Torr. - IR: 1740 cm^{-1} (COOR). - ^1H NMR: δ = 1.06 (d, J = 7 Hz, 2-Me), 1.31 (s, 7-Me); 1.86, 1.99 (ABdd, J = 14, 10, 6 Hz), 2.39, 2.45 (ABdd, J = 16, 10, 6 Hz), 1.25 (t), 4.14 (q, J = 7 Hz), CH_2CH_2COOEt. - ^{13}C NMR: δ 17.2, 21.2 (2 q, 2-, 7-Me), 24.4, 25.0, 28.2, 33.1 (4 t, C-3-6), 39.0 (d, C-7), 65.3, 67.9 (2 s, C-1, -2); 31.0, 36.3, 60.3 (3 t), 14.3 (q), 173.3 (s); CH_2CH_2COOEt. - MS: m/z (%): 240 (M^+, 4), 222 (7), 195 (9), 129 (45), 111 (95), 69 (100), 55 (100). - $C_{14}H_{24}O_3$ calcd. C 69.96, H 10.07, found C 69.82, H 10.00.

trans- (11a) and cis-2,7-Dimethyl-1-(3-hydroxypropyl)-1-cycloheptanol (11b):

The 11a,b-mixture (2:1) was prepared according to ref.[7]. - FC of the crude product with ether afforded (as 1. fraction) crystals of pure 11b, m.p. 66°C. - ^1H NMR [D_6-DMSO]: δ = [0.84] 0.96 (d, J = 7 Hz, 2-, 7-Me), 1.32 (d, br., J = 13 Hz, 1 H), 3.62 [4.37] (t, J = 6.5 Hz, CH_2OH). - ^{13}C NMR: δ = 18.1 (q, 2-, 7-Me), 25.6, 30.1 (2 t, C-3-6), 40.3 (d, C-2, -7), 76.5 (s, C-1); 27.3, 35.6, 63.2 (3 t, $CH_2CH_2CH_2OH$). - MS: m/z (%): 200 (M^+, 1), 141 (22), 129 (34), 111 (100), 97 (62), 69 (54). - A mixture of 11a,b was obtained as 2. fraction. - ^1H NMR [D_6-DMSO] of 11a: [0.87, 0.89] 0.975, 0.98 (2 d, J = 7 Hz, 2-, 7-Me), 3.63 [4.37] (t, J = 6.5 Hz, CH_2OH).

trans- (12a) and cis-6,11-Dimethyl-1-oxaspiro[4.6]undecan-2-one (12b):

To a solution of 1.5 g (7.5 mmol) of 11a,b in 25 ml of acetone at 0°C 2.75 ml of Jones reagent were added within 30 min. Stirring was continued for 15 min, then solid $NaHSO_3$ was added. After addition of 50 ml of brine the mixture was extracted with ether. - Distillation gave 0.68 g (46%) of 12a,b (2:1), b.p. 100°C/0.2 Torr (ref.[7] 140-142°C/5 Torr). - IR ($CHCl_3$): 1750 cm^{-1} (γ-lactone) (ref.[7] 1760 cm^{-1}). - Repeated FC (PE/20% ether → ether) gave (as 1. fraction) 12a, oil. - ^1H NMR: δ = 0.91, 0.98 (2 d, J = 7 Hz, 6-, 11-Me), 1.91, 2.15 (AB, J = 13.5 Hz, A-part dd, J = 11, 7.5, B-part dd, J = 10, 6.5 Hz, 4-H_2), 2.54, 2.55 (AB, J = 19, A-part dd, J = 11, 6.5, B-part dd, J = 10, 7.5 Hz, 3-H_2). (ref.[7] in CCl_4: 0.89, 1.0). - ^{13}C NMR: δ = 16.4, 16.9 (2 q, 6-, 11-Me), 26.9, 27.3, 27.7, 29.8, 29.9, 30.1 (6 t, C-3, -4, -7-10), 40.8, 44.1 (2 d, C-6, -11), 93.8 (s, C-5), 177.4 (s, C-2). - MS: m/z (%): 196 (M^+, 10), 153 (14), 139 (10), 125 (100), 112 (20), 97 (15), 68 (14), 55 (28).

12b (with 10% of 12a), oil, was isolated as 2. fraction (ref.[7] m.p. 34-36°C). - ^1H NMR: δ = 0.98 (d, J = 7 Hz, 6-, 11-Me), 2.09 (dd, J = 10, 8 Hz, 4-H_2), 2.54 (dd, J = 10, 8 Hz, 3-H_2). (ref.[7] in CCl_4: 0.904, 1.0). - ^{13}C NMR: δ = 17.8 (q, 6-, 11-Me), 25.0, 29.5 (2 t, C-7-10), 44.3 (d, C-6, -11), 29.2 (t, C-4), 32.3 (t, C-3), 92.3 (s, C-5), 177.8 (s, C-2).

Solvolysis of 9a with H_2SO_4:

A solution of 2.4 g (10 mmol) of 9a[10] in 30 ml of acetone and 2 ml of 2 N H_2SO_4 was refluxed for 4 h. After cooling some K_2CO_3 (for neutralization and drying) was added. - Repeated FC (benzene/ether 2:1 → 1:9) afforded (as 1. fraction) 0.74 g (35%) of (5R*,6R*,11R*)-6-Hydroxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2-one (10a)

m.p. 75°C (PE). - IR: 3600, 3460 (OH), 1765 cm^{-1} (γ-lactone) (ref.[7] 1760). - ^1H NMR: δ = 1.03 (d, J = 7 Hz, 11-Me), 1.31 (s, 6-Me), 1.86, 1.96 (2 mc, 4-H_2, 11-H), 2.58 (mc, 3-H_2). - NOED spectrum: ↓ 6-Me → NOE 11-Me, ↓ 11-Me → NOE 6-Me. - ^1H NMR (90 MHz, CCl_4): δ = 1.02, 1.29 (ref.[7] 0.9, 1.4). - ^{13}C NMR: δ = 17.6, 26.2 (2 q, 6-, 11-Me), 20.8, 24.0, 29.1, 29.5, 29.6, 36.0 (6 t, C-3, -4, -7-10), 40.8 (d, C-11), 77.1 (s, C-6), 94.3 (s, C-5), 178.1 (s, C-2). - MS: m/z (%): no M^+, 194 (M -H_2O, 62), 179 (14), 154 (53), 125 (73), 109 (73), 96 (89), 71 (75), 55 (100). - $C_{12}H_{20}O_3$ calcd. C 67.89, H 9.50, found C 67.77, H 9.43.

1.07 g (51%) of (5S*,6S*,11R*)-6-Hydroxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2-one (10b), m.p. 89°C (PE), were isolated as 2. fraction. - IR: 3600, 3460 (OH), 1765 cm^{-1} (γ-lactone). - ^1H NMR: δ = 0.93 (d, J = 7 Hz, 11-Me), 1.39 (s, 6-Me), 1.96, 2.38 (AB, J = 13, A-part dd, J = 11, 6, B-part dd, J = 11.5, 5.5 Hz, 4-H_2), 2.47, 2.68 (AB, J = 19 Hz, A-part dd, J = 11, 5.5 Hz, B-part dd, J = 11.5, 6 Hz, 3-H_2), 2.03 (mc, 11-H). - NOED spectrum: ↓ 6-Me → NOE 6-OH, 11-H, ↓ 11-Me → NOE 4-H, 6-OH. - ^{13}C NMR: δ = 17.6, 22.9 (2 q, 6-, 11-Me), 20.9, 21.4, 25.1, 30.0, 30.6, 36.9 (6 t, C-3, -4, -7-10), 37.1 (d, C-11), 77.8 (s, C-6), 96.2 (s, C-5), 178.2 (s, C-2). - MS: m/z (%): 212 (M^+, 0.4), 194 (62), 179 (13), 154 (82), 125 (53), 109 (50), 86 (70), 71 (100), 55 (64). - $C_{12}H_{20}O_3$ calcd. C 67.89, H 9.50, found C 67.72, H 9.55.

Solvolysis of 9a with NaOH, then HCl:

According to ref.[7] 2.4 g (10 mmol) of 9a[10] were refluxed for 2 h with NaOH (5%), then warmed to 50°C for 30 min with HCl (10%) to give 1.74 g (82%) of 10a,b,c (2:1:0.1). - FC (PE/40% ether → ether) afforded 40 mg of 10a/c (2:1), 1. fraction, 1.1 g of 10a/b (2:1), 2. fraction, 0.3 g of 10a/b (1:1), 3. fraction.

(5S*,6R*,11R*)-6-Hydroxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2-one (10c):

A solution of 0.12 g (0.5 mmol) of 8 in 1 ml of pyridine was treated with 0.12 g (0.47 mmol) of OsO_4 in 1.5 ml of pyridine. After stirring for 1 h a mixture of 0.85 g of $NaHSO_3$, 2.5 ml of pyridine and 3.5 ml of water was added and stirred for

30 min. Then the mixture was acidified with icecold H_2SO_4 (10%) and extracted with $CHCl_3$. - The crude ethyl (r-1,c-2-dihydroxy-t-2,t-7-dimethylcyclohept-1-yl)propanoate (7) (^{1}H NMR: δ = 0.97 (d, J = 7 Hz, 7-Me), 1.25 (s, 2-Me); $CH_2CH_2CO_2Et$: 1.90 (t, J = 8 Hz), 2.48, 2.52 (ABt, J = 17, 8 Hz), 1.24 (t, J = 7 Hz), 4.13 (q, J = 7 Hz) was chromatographed on alumina (PE/ether 1:1) to furnish 83 mg (83%) of oily 10c (ref.[7] b.p. 130°C/0.1 Torr). - IR: 3680, 3580 (OH), 1765 cm^{-1} (γ-lactone) (ref.[7] 3620, 1760). - ^{1}H NMR: δ = 0.87 (d, J = 7 Hz, 11-Me), 1.20 (s, 6-Me), 1.90, 2.13 (AB, J = 14, A-part dd, J = 10.5, 6.5, B-part dd, J = 10.5, 8.5 Hz, 4-H_2), 2.60 (mc, 3 H) (ref.[7] 0.9 (d, 7), 1.3 (s)). - NOED spectrum: ↓ 11-Me → NOE 6-Me, 4-H, ↓ 6-Me → NOE 11-Me, 4-H', 3-H). - ^{13}C NMR: δ = 17.3, 26.3 (2 q, 6-, 11-Me), 20.0, 22.5, 24.9, 29.9, 30.1, 36.9 (6 t, C-3, -4, -7-10), 34.7 (d, C-11), 76.9 (s, C-6), 95.8 (s, C-5), 176.7 (s, C-2). - MS: m/z (%): no M^+, 194 (18), 166 (15), 154 (56), 124 (32), 109 (32), 99 (43), 86 (50), 71 (100), 69 (54), 57 (59), 55 (80). $C_{12}H_{20}O_3$ calcd. C 67.89, H 9.50, found C 67.85, H 9.42.

Dehydration of 10, general procedure:

To a solution of 3.32 g (14 mmol) of Burgess' reagent[11] in 35 ml of benzene a solution of 2.12 g (10 mmol) of 10 in 20 ml of benzene was added dropwise. After stirring for 4 h at 60°C the mixture was poured into 30 ml of water. Work-up (ether) and distillation (b.p. 100°C/0.02 Torr) yielded mixtures of 13/14. - Pure 13 was isolated in the next step (see below).

(5R*,11R*)-11-Methyl-6-methylidene-1-oxaspiro[4.6]undecan-2-one (13a) and 14a:

From 10a, yield 1.78 g (92%) of 13a/14a (1:2). - IR: 1780 cm^{-1} (γ-lactone). - ^{1}H NMR (13a): δ = 0.99 (d, J = 7 Hz, 11-Me), 2.09, 2.14, 2.45, 2.55 (ABCD, J_{AB} = 13, J_{AC} = 12, J_{AD} = 10, J_{BC} = 9, J_{BD} = 11, J_{CD} = 19 Hz, 3-, 4-CH_2), 4.92, 5.00 (2 s, br., H_2C=). - ^{13}C NMR: δ = 16.1 (q, 11-Me), 27.9, 28.5, 31.4, 31.5, 32.0, 32.2 (6 t, C-3, -4, -7-10), 42.1 (d, C-11), 91.8 (s, C-5), 111.3 (t, $=CH_2$), 151.2 (s, C-6), 177.4 (s, C-2). - $C_{12}H_{18}O_2$ calcd. C 74.19, H 9.34, found C 74.04, H 9.27.

(5R*,11R*)-6,11-Dimethyl-1-oxaspiro[4.6]undec-6-en-2-one (14a), NMR data from the mixture with 13a: ^{1}H NMR: δ = 1.09 (d, J = 7 Hz, 11-Me), 1.70 (t, J = 1.5 Hz, 6-Me), 5.64 (tq, J = 7, 1.5 Hz, 7-H). - ^{13}C NMR: δ = 13.9, 23.9 (2 q, 6-, 11-Me), 20.2, 27.4, 29.5, 31.9, 33.5 (5 t, C-3, -4, -8-10), 39.8 (d, C-11), 94.3 (s, C-5), 124.6 (d, C-7), 141.0 (s, C-6), 176.9 (s, C-2).

(5S*,11R*)-11-Methyl-6-methylidene-1-oxaspiro[4.6]undecan-2-one (13b) and 14b:

From 10b, yield 1.76 g (91%) of 13b/14b (1:6). - IR: 1780 cm^{-1} (γ-lactone). - ^{1}H NMR (13b): δ = 0.94 (d, J = 7 Hz, 11-Me), 4.98 (dd, J = 3, 1 Hz), 5.06 (d, J = 1 Hz, H_2C=). - ^{13}C NMR: δ = 16.1 (q, 11-Me), 23.4, 26.8, 28.1, 29.1, 32.1, 32.4 (6 t, C-3, -4, -7-10), 42.2 (d, C-11), 93.1 (s, C-5), 113.1 (t, CH_2=), 149.3 (s, C-6), 176.9 (s, C-2). - $C_{12}H_{18}O_2$ calcd. C 74.19, H 9.34, found C 74.22, H 9.29.

(5S*,11R*)-6,11-Dimethyl-1-oxaspiro[4.6]undec-6-en-2-one (14b), NMR data from the mixture with 13b: ^{1}H NMR: δ = 0.93 (d, J = 7 Hz, 11-Me), 1.75 (dd, J = 2.5, 1.5 Hz, 6-Me), 2.14, 2.29, 2.52, 2.55 (ABCD, J_{AB} = 13, J_{AC} = 5, J_{AD} = 10, J_{BC} = 10, J_{CD} = 18 Hz, 3-, 4-CH_2), 5.69 (tq, J = 7, 1.5 Hz, 7-H). - ^{13}C NMR: δ = 16.9 , 22.5 (2 q, 6-, 11-Me), 26.1, 27.1, 27.7, 29.5, 34.0 (5 t, C-3, -4, -8-10), 38.8 (d, C-11), 92.4 (s, C-5), 127.7 (d, C-7), 142.5 (s, C-6), 176.7 (s, C-2).

From 40 mg of 10c 30 mg (83%) of 13b/14b (1:1) were obtained.

Oxidation of 13/14, general procedure:

12.0 g (0.12 mol) of dry CrO_3 were added at 10°C successively to a mixture of 200 ml of CH_2Cl_2 and 18.9 g (0.24 mol) of pyridine under vigorous stirring. After 20 min at room temp. a solution of 3.88 g (20 mmol) of the 13/14-mixture in 20 ml of CH_2Cl_2 was added dropwise. After stirring for 1 d the mixture was filtered, and the residue was washed with ether. The organic phase was washed successively with 200 ml of NaOH (5%), 200 ml of HCl (5%), and 200 ml of saturated $NaHCO_3$ solution.- - FC (ether) afforded unchanged 13, then with ether/methanol (50:1) 15.

(5R*,11R*)-6,11-Dimethyl-1-oxaspiro[4.6]undec-6-en-2,8-dione (15a):

From 13a/14a, yield 2.07 g (50%), m.p. 92°C (ether). - IR: 1785 (γ-lactone), 1675, 1625 cm^{-1} (C=C-C=O). - ^{1}H NMR: δ = 1.16 (d, J = 7 Hz, 11-Me), 1.79, 2.09 (AB, J = 15, A-part ddd, J = 8, 5, 4, B-part ddd, J = 10, 4, 4 Hz, 10-H_2), 2.20 (mc, 11-H), 2.21, 2.41 (AB, J = 13, A-part t, J = 8, B-part dd, J = 9, 8, 4-H_2), 2.52, 2.67 (AB, J = 16, A-part dd, J = 8, 4, B-part dd, J = 10, 5 Hz, 9-H_2), 2.60 (tdd, J = 8, 9, 8 Hz, 3-H_2), 1.93 (d, J = 1.5 Hz, 6-Me), 5.93 (q, J = 1.5 Hz, 7-H). - ^{13}C NMR: δ = 15.5, 23.1 (2 q, 6-, 11-Me), 26.4, 28.7, 35.2, 39.4 (4 t, C-3, -4, -9, -10), 40.7 (d, C-11), 92.1 (s, C-5), 128.4 (d, C-7), 152.6 (s, C-6), 175.6 (s, C-2), 202.9 (s, C-8). - MS: m/z (%): 208 (M^+, 7), 180 (7), 166 (64), 138 (32), 124 (46), 111 (100), 110 (46), 96 (40), 95 (50), 82 (40), 69 (38), 56 (80), 55 (100), 53 (57). $C_{12}H_{16}O_3$ calcd. C 69.21, H 7.74, found C 69.33, H 7.81.

(5S*,11R*)-6,11-Dimethyl-1-oxaspiro[4.6]undec-6-en-2,8-dione (15b):

From 13b/14b, yield 2.32 g (56%), m.p. 112°C (ether). - IR: 1785 (γ-lactone), 1675, 1630 cm^{-1} (C=C-C=O). - ^{1}H NMR: δ = 1.02 (d, J = 7 Hz, 11-Me), 1.66, 1.92 (AB, J = 15, A-part ddd, J = 10, 5, 5, B-part ddd, J = 8, 5, 5 Hz, 10-H_2), 1.97 (d, J = 1.5

Hz, 6-Me), 2.21, 2.40 (AB, J = 14, A-part, dd, J = 10, 6, B-part dd, J = 10, 10 Hz, 4-H_2), 2.35 (mc, 11-H), 2.51, 2.68 (AB, J = 16, A-part dd, J = 8, 5, B-part dd, J = 10, 5 Hz, 9-H_2), 2.63, 2.64 (AB, J = 17, A-part dd, J = 10, 6, B-part dd, J = 10, 10 Hz, 3-H_2), 5.95 (q, J = 1.5 Hz, 7-H). - ^{13}C NMR: δ = 16.8, 22.8 (2 q, 6-, 11-Me), 27.1, 28.3, 29.0, 40.6 (4 t, C-3, -4, -9, -10), 40.8 (d, C-11), 90.9 (s, C-5), 129.8 (d, C-7), 154.0 (C-6), 175.6 (C-2), 202.0 (C-8). - MS: m/z (%): 208 (M^+, 15), 180 (12), 166 (66), 138 (30), 124 (40), 111 (100), 110 (40), 95 (42), 55 (58). - $C_{12}H_{16}O_3$ calcd. C 69.21, H 7.74, found C 69.15, H 7.62.

Reduction of the ketones 15, general procedure:

The solution of 0.52 g (2.5 mmol) of 15 in 10 ml of methanol was cooled to 0°C and treated with 0.1 g (2.5 mmol) of $NaBH_4$. After stirring for 30 min at 0°C and 5 h at room temp. 0.1 ml of acetic acid was added, the solvent removed, the mixture poured into 10 ml of water and extracted with ether.

(5R*,8R*,11R*)-8-Hydroxy-6,11-dimethyl-1-oxaspiro[4.6]undec-6-en-2-one (16a):

From 15a, FC afforded 0.50 g (92%) of oily 16a (containing 20% of 17a). - IR: 3600, 3450 (OH), 1770 cm^{-1} (γ-lactone). - ^{1}H NMR: δ = 1.12 (d, J = 7 Hz, 11-Me), 1.75 (dd, J = 1.5, 1.5 Hz, 6-Me), 2.33, 2.54 (2 mc, 3-, 4-H_2), 4.36 (ddd, br., J = 11, 5, 2.5 Hz, 8-H), 5.57 (dq, J = 2.5, 1.5 Hz, 7-H). - MS: m/z (%): 210 (M^+, 5), 182 (22), 166 (13), 125 (100), 111 (58), 83 (38), 55 (35). - $C_{12}H_{18}O_3$ calcd. C 68.54, H 8.63, found C 68.31, H 8.50.
^{1}H NMR of the (5R*,8S*,11R*)-isomer 17a (from the mixture): δ = 1.08 (d, J = 7 Hz, 11-Me), 1.78 (dd, J = 2, 1.5 Hz, 6-Me), 4.27 (ddd, br., J = 7, 7, 2 Hz, 8-H), 5.73 (dq, J = 7, 2 Hz, 7-H).

(5S*,8S*,11R*)-8-Hydroxy-6,11-dimethyl-1-oxaspiro[4.6]undec-6-en-2-one (16b):

From 15b, crystallization (ether) gave 0.46 g (84%) of 16b, m.p. 103°C. - IR: 3600, 3450 (OH), 1770 cm^{-1} (γ-lactone). - ^{1}H NMR: δ = 0.89 (d, J = 7 Hz, 11-Me), 1.58, 1.86 (AB, J = 12, A-part ddd, J = 10, 10, 2 Hz, B-part br., 10-H_2), 1.64, 1.80 (AB, J = 12, A-part ddd, J = 10, 10, 2 Hz, B-part br., 9-H_2), 1.78 (dd, J = 1.5, 1.5 Hz, 6-Me), 2.10 (dqdd, J = 10, 7, 4, 4 Hz, 11-H), 2.31 (ddd, J = 13, 10, 10 Hz, 4-H_2), 2.50, 2.52 (AB, J = 18, A-part ddd, 10, 10, 4, B-part dd, J = 10, 10 Hz, 3-H_2), 4.31 (dddq, J = 10, 3, 1.5, 1.5 Hz, 8-H), 5.60 (dq, J = 3, 1.5 Hz, 7-H). - ^{13}C NMR: δ = 17.3, 23.1 (2 q, 6-, 11-Me), 27.6, 29.3, 30.9, 36.5 (4 t, C-3, -4, -9,-10), 38.7 (d, C-11), 69.9 (d, C-8), 92.1 (s, C-5), 132.9 (d, C-7), 141.6 (s, C-6), 176.8 (s, C-2). - MS: m/z (%): 210 (M^+, 4), 182 (20), 125 (100), 109 (20), 97 (24), 69 (24), 55 (34). - $C_{12}H_{18}O_3$ calcd. C 68.54, H 8.63, found C 68.49, H 8.72.
^{1}H NMR of the (5S*,8R*,11R*)-isomer 17b (from the mother liquor): δ = 0.94 (d, J = 7 Hz, 11-Me), 5.70 (mc, 7-H).

(5R*,6R*,7R*,8R*,11R*)-6,7-Epoxy-8-hydroxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2-one (18a): Prepared according to the procedure described for 6 from 0.40 g (1.9 mmol) of 16a (with 20% 17a) and 0.45 g (2.2 mmol) of mCPBA, 2 d at room temp. - FC (ether) furnished 0.34 g (79%) of oily 18a (containing 20% of 18a'). - IR: 3600, 3450 (OH), 1770 cm^{-1} (γ-lactone). - ^{1}H NMR: δ = 1.20 (d, J = 7 Hz, 11-Me), 1.38 (s, 6-Me), 1.83, 2.35 (AB, J = 12, A-part dd, J = 12, 8, B-part dd, J = 9, 2 Hz, 4-H_2), 2.02 (dqd, J = 11, 7, 4 Hz, 11-H), 2.45, 2.69 (AB, J = 18, A-part dd, J = 8, 2, B-part dd, J = 12, 9 Hz, 3-H_2), 2.99 (d, J = 6 Hz, 7-H), 3.62 (ddd, J = 13, 6, 2.5 Hz, 8-H). - MS: m/z (%): no M^+, 211 (3), 165 (13), 156 (97), 139 (100), 111 (80), 75 (70), 55 (60). - $C_{12}H_{18}O_4$ calcd. C 63.70, H 8.02, found C 63.47, H 8.15.
^{1}H NMR of the (5R*,6S*,7S*,8S*,11R*)-isomer 18a' (from the mixture): δ = 1.14 (d, J = 7 Hz, 11-Me), 1.37 (s, 6-Me), 3.07 (d, J = 4 Hz, 7-H), 4.32 (ddd, J = 8, 4, 2 Hz, 8-H).

(5S*,6S*,7S*,8S*,11R*)-6,7-Epoxy-8-hydroxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2-one (18b): From 0.72 g (3.4 mmol) of 16b and 0.81 g (4.0 mmol) of mCPBA, 2 d at room temp. - Crystallization (ether) gave 0.55 g (70%) of 18b, m.p. 122°C. - IR: 3600, 3450 (OH), 1770 cm^{-1} (γ-lactone). - ^{1}H NMR: δ = 0.95 (d, J = 7 Hz, 11-Me), 1.34 (s, 6-Me), 1.89, 2.04 (AB, J = 13, A-part dd, J = 11, 9, B-part dd, J = 10, 2 Hz, 4-H_2), 2.13 (dqd, J = 12, 7, 2 Hz, 11-H), 2.41, 2.66 (AB, J = 18, A-part dd, J = 9, 2, B-part dd, J = 10, 11 Hz, 3-H_2), 2.94 (d, J = 6 Hz, 7-H), 3.65 (ddd, J = 12, 6, 2 Hz, 8-H). - ^{13}C NMR: δ = 16.4, 19.9 (2 q, 6-, 11-Me), 23.6, 29.0, 30.4, 34.0 (4 t, C-3, -4, -9, -10), 38.2 (d, C-11), 62.6 (s, C-6), 68.4, 70.6 (2 d, C-7, -8), 91.1 (s, C-5), 176.6 (s, C-2). - MS: m/z (%): 226 (M^+, 0.2), 211 (6), 165 (18), 138 (18), 112 (78), 97 (52), 57 (65), 55 (100). - $C_{12}H_{18}O_4$ calcd. C 63.70, H 8.02, found C 63.82, H 8.25.

Jones oxidation of 18, general procedure:

To a solution of 0.34 g (1.5 mmol) of 18 in 5 ml of acetone 0.5 ml of Jones reagent was added dropwise (syringe) at 0°C. Stirring was continued for 1.5 h, then isopropanol was added to destroy excess reagent. - After work-up 19 crystallized from ether.

(5R*,6R*,7S*,11R*)-6,7-Epoxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2,8-dione (19a):

From 18a, yield 0.23 g (68%), m.p. 123°C. - IR: 1785 (γ-lactone), 1715 cm^{-1} (CO). - ^{1}H NMR: δ = 1.19 (d, J = 7 Hz, 11-Me), 1.48 (s, 6-Me), 1.65-1.85 (m, 10-H_2), 1.95, 2.32 (AB, J = 13, A-part dd, J = 9, 9, B-part dd, J = 9, 4 Hz, 4-H_2), 2.16

(qdd, J = 7, 5, 3.5 Hz, 11-H), 2.45, 2.70 (AB, J = 13, A-part dd, J = 7, 5, B-part dd, J = 10, 5 Hz, 9-H_2), 2.52, 2.69 (AB, J = 18, A-part dd, J = 9, 4, B-part dd, J = 9, 9 Hz, 3-H_2), 3.45 (s, 7-H). - ^{13}C NMR: δ = 15.1, 21.9 (2 q, 6-, 11-Me), 26.0, 28.9, 30.3, 36.6 (4 t, C-3, -4, -9, -10), 40.8 (d, C-11), 62.4 (s, C-6), 66.2 (d, C-7), 90.0 (s, C-5), 176.2 (s, C-2), 205.3 (s, C-8). - MS: m/z (%): 224 (M^+, 1), 209 (1.5), 182 (28), 156 (20), 154 (20), 139 (48), 125 (100), 112 (58), 100 (52), 85 (51), 55 (90). - $C_{12}H_{16}O_4$ calcd. C 64.27, H 7.19, found C 64.06, H 7.10

(5S*,6S*,7R*,11R*)-6,7-Epoxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2,8-dione (19b):

From 18b, yield 0.33 g (98%), m.p. 105°C. - IR: 1775 (γ-lactone), 1720 cm^{-1} (CO). - ^{1}H NMR: δ = 1.01 (d, J = 7 Hz, 11-Me), 1.46 (s, 6-Me), 1.6-1.75 (m, 10-H_2), 2.05, 2.59 (AB, J = 13, A-part dd, J = 10, 9, B-part dd, J = 5, 5 Hz, 9-H_2), 2.09 (dqd, J = 13, 7, 3 Hz, 11-H), 2.19, 2.60 (AB, J = 14, A-part dd, J = 10, 4, B-part dd, J = 10, 9 Hz, 4-H_2), 2.51, 2.70 (AB, J = 18, A-part dd, J = 10, 4, B-part dd, J = 10, 9 Hz, 3-H_2), 3.40 (s, 7-H). - ^{13}C NMR: δ = 16.1, 20.2 (2 q, 6-, 11-Me), 24.5, 26.0, 29.0, 39.4 (4 t, C-3, -4, -9, -10), 39.2 (d, C-11), 65.7 (s, C-6), 66.2 (d, C-7), 89.6 (s, C-5), 176.0 (s, C-2), 205.5 (s, C-8). - MS: m/Z (%): 224 (M^+, 0.1), 209 (1), 182 (16), 154 (17), 139 (31), 125 (100), 112 (55), 100 (46), 85 (80), 55 (88). - $C_{12}H_{16}O_4$ calcd. C 64.27, H 7.19, found C 64.38, H 7.26.

Wittig-Horner reaction of 19, general procedure:

As described for 5 0.35 g (1.8 mmol) of trimethyl phosphonopropionate in 1.5 ml of dioxane was added dropwise (syringe) to 54 mg (1.8 mmol) of NaH in 3 ml of dioxane. After 30 min at room temp. 0.21 g (0.94 mmol) of 19 in 1.5 ml of dioxane was added. It was stirred for 2 d, then quenched with water and extracted with ether. - FC (PE/ether 1:3) of the product gave 20.

Methyl (5R*,6R*,7R*,11R*)-2-(6,7-epoxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2-on-8-ylidene)-propionate (20a):

From 19a. - 1. Fraction: 25 mg (9%) of (E)-20a. - ^{1}H NMR: δ = 1.24 (d, J = 7 Hz, 11-Me), 1.45 (s, 6-Me), 1.69, 1.86 (AB, J = 14, A-part ddd, 5, 4, 3, B-part ddd, 14, 4, 3 Hz, 10-H_2), 1.78, 2.17 (AB, J = 13, A-part dd, J = 11, 9, B-part dd, J = 9, 2 Hz, 4-H_2), 2.01 (dd, J = 1, 1.5 Hz, Me-C=), 2.07 (dqd, J = 14, 7, 4 Hz, 11-H), 2.03, 2.78 (AB, J = 14, A-part dd, J = 4, 3, B-part dd, J = 5, 3 Hz, 9-H_2), 2.39, 2.68 (AB, J = 18, A-part dd, J = 9, 2, B-part dd, J = 11, 9 Hz, 3-H_2), 3.46 (s, br., 7-H), 3.75 (s, OMe).

2. Fraction: 170 mg (62%) of (Z)-20a. - IR: 1770 (γ-lactone), 1715, 1665 cm^{-1} (C=C-COOR). - ^{1}H NMR: δ = 1.24 (d, J = 7 Hz, 11-Me), 1.42 (s, 6-Me), 1.65, 1.85 (AB, J = 12, A-part ddd, J = 4, 4, 3, B-part dddd, J = 13, 11, 3, 2 Hz, 10-H_2), 1.88 (dd, J = 2, 1 Hz, Me-C=), 1.70, 2.17 (AB, J = 12, A-part dd, J = 9, 9, B-part dd, J = 9, 3 Hz, 4-H_2), 2.04 (dqd, J = 11, 7, 4 Hz, 11-H), 2.15, 2.39 (AB, J = 14, A-part dd, J = 13, 3, B-part dd, J = 4, 3 Hz, 9-H_2), 2.35, 2.62 (AB, J = 17, A-part dd, J = 9, 3, B-part dd, J = 11, 9 Hz, 3-H_2), 3.62 (q, J = 2 Hz, 7-H), 3.79 (s, OMe). - ^{13}C NMR: δ = 14.4, 21.9 (2 q, 6-, 11-Me), 24.2, 29.2, 29.4, 31.2 (4 t, C-3, -4, -9, -10), 40.8 (d, C-11), 62.1 (s, C-6), 62.8 (d, C-7), 91.3 (s, C-5), 140.1 (s, C-8), 176.8 (s, C-2), =C(Me)-COOMe: 128.1 (s), 15.2 (q), 170.0 (s), 52.0 (q). - MS: m/z (%): 294 (M^+, 3), 251 (5), 219 (5), 167 (5), 139 (9), 126 (100), 125 (35), 55 (18). - $C_{16}H_{22}O_5$ calcd. C 65.29, H 7.53, found C 65.12, H 7.45.

Methyl (5S*,6S*,7S*,11R*)-2-(6,7-epoxy-6,11-dimethyl-1-oxaspiro[4.6]undecan-2-on-8-ylidene)-propionate (20b):

From 19b. - 1. Fraction: 31 mg (11%) of (E)-20b. - ^{1}H NMR: δ = 0.94 (d, J = 7 Hz, 11-Me), 1.45 (mc, 1 H), 1.46 (s, 6-Me), 1.8 (mc, 4 H), 2.02 (s, br., Me-C=), 2.24 (dqd, J = 12, 7, 4 Hz, 11-H), 2.34, 2.66 (AB, J = 18, A-part dd, J = 8, 3, B-part dd, J = 11, 10 Hz, 3-H_2), 2.95 (ddd, J = 13, 5, 3 Hz, 9-H), 3.41 (s, br., 7-H), 3.74 (s, OMe).

2. Fraction: 185 mg (67%) of (Z)-20b. - IR: 1765 (γ-lactone), 1715, 1670 cm^{-1} (C=C-COOR). - ^{1}H NMR: δ = 0.94 (d, J = 7 Hz, 11-Me), 1.23, 1.80 (AB, J = 12, A-part ddd, J = 13, 13, 3, B-part ddd, J = 5, 4, 3 Hz, 10-H_2), 1.43 (s, 6-Me), 1.71, 1.81 (AB, J = 13, A-part dd, J = 11, 9, B-part dd, J = 9, 2 Hz, 4-H_2), 1.86 (dd, J = 2, 1 Hz, Me-C=), 1.94, 2.55 (AB, J = 12, A-part dd, br., J = 13, 3, B-part dd, J = 5, 3 Hz, 9-H_2), 2.22 (dqd, J = 13, 7, 4 Hz, 11-H), 2.31, 2.60 (AB, J = 18, A-part dd, J = 9, 2, B-part dd, J = 11, 9 Hz, 3-H_2), 3.55 (q, J = 2 Hz, 7-H), 3.80 (s, OMe). - ^{13}C NMR: δ = 14.3, 19.0 (2 q, 6-, 11-Me), 23.7, 29.0, 29.6, 31.0 (4 t, C-3, -4, -9, -10), 37.9 (d, C-11), 62.6 (d, C-7), 63.7 (s, C-6), 91.3 (s, C-5), 139.7 (s, C-8), 176.7 (s, C-2), =C(Me)-COOMe: 127.5 (s), 16.1 (q), 169.9 (s), 52.0 (q). - MS: m/z (%): 294 (M^+, 2), 251 (5), 219 (6), 167 (4), 139 (7), 127 (13), 126 (100), 125 (38). - $C_{16}H_{22}O_5$ calcd. C 65.29, H 7.53, found C 65.25, H 7.38

Hydrolysis of (Z)-20, general procedure:

As described for 9a 0.16 g (0.54 mmol) of 20 in 1 ml of acetone and 0.06 ml of 2 N H_2SO_4 was stirred at room temp. for 1 d. Some K_2CO_3 (for neutralization and drying) then ether was added. After filtration and evaporation the residue was recrystallized from ether/acetone.

(6R*,7R*,8R*,8aS*)-3',4',5,6,8,8a-Hexahydro-8-hydroxy-3,6,8-trimethylspiro[7H-cyclohepta[b]furan-7,2'(5'H)-furan]-2,5'(4H)-dione (rac. isocanambrin, 1):

From (Z)-20a, yield 103 mg (68%), m.p. 210°C (ether/acetone 10:1), [ref.[3] m.p. 240-242°C for (-)-1]. - IR ($CHCl_3$): 3600 (OH), 1780-1745 (γ-lactone, butenolide), 1670 cm^{-1} (C=C), [ref.[3] 3600, 1765 cm^{-1}]. - ^1H NMR: δ = 1.11 (s, 8-Me), 1.13 (d, J = 7 Hz, 6-Me), 1.84 (ddd, J = 1.5, 1.5, 1.5 Hz, 3-Me), 2.22 (qdd, J = 7, 7, 2 Hz, 6-H), 2.60, 2.77 (AB, br., J = 20, B-part d, br., J = 12 Hz, 4-H_2), 4.96 (q, J = 1.5 Hz, 8a-H), [ref.[3] 1.13 (s), 1.16 (d, J = 7 Hz), 1.86 (d, J = 2 Hz), 5.01 (d, br., J = 2 Hz]. - ^1H NMR ($CDCl_3/C_6D_6$ 3:2, with spin decoupling): δ = 0.90 (d, J = 7 Hz, 6-Me), 0.91 (s, 8-Me), 1.43 (mc, 5-H_2), 1.52, 2.53 (AB, J = 11, A-part dd, J = 11, 8, B-part dd, J = 11, 3.5 Hz, 4'-H_2), 1.65 (d, br., J = 1.5 Hz, 3-Me), 1.84 (qdd, J = 7, 7, 2 Hz, 6-H), 2.13, 2.35 (AB, br., J = 20, B-part br., d, J = 12 Hz, 4-H_2), 2.29, 2.69 (AB, J = 17, A-part dd, J = 11, 3.5, B-part dd, J = 11, 8 Hz, 3'-H_2), 4.66 (d, br., J = 1.5 Hz, 8a-H). - NOED-spectrum: ↓ 8a-H → NOE 8-OH, 3'-H, ↓8-OH → NOE 8a-H, 8-Me, 3'-H, ↓ 8-Me → NOE 8-OH. -- ^{13}C NMR: δ = 8.6, 14.1, 18.4 (3 q, 3-, 6-, 8-Me), 21.7, 23.7, 29.7, 31.2 (4 t, C-4, -5, -3', -4'), 42.6 (d, C-6), 79.3 (s, C-8), 84.0 (d, C-8a), 91.9 (s, C-7), 124.8 (s, C-3), 160.0 (s, C-3a), 173.8 (s, C-2), 177.4 (s, C-2'). - MS: m/z (%): 280 (M^+, 33), 262 (13), 247 (8), 237 (14), 220 (48), 219 (37), 202 (28), 177 (40), 125 (87), 112 (100), 110 (42), 69 (85), 55 (57). - $C_{15}H_{20}O_5$ calcd. C 64.27, H 7.19, found C 64.11, H 7.08.

(6R*,7S*,8S*,8aR*)-3',4',5,6,8,8a-Hexahydro-8-hydroxy-3,6,8-trimethylspiro[7H-cyclohepta[b]furan-7,2'(5'H)-furan]-2,5'(4H)-dione (rac. 6-epi-isocordilin, 21):

From (Z)-20b, yield 127 mg (81%), m.p. 249°C (ether/acetone 7:1). - IR ($CHCl_3$): 3590 (OH), 1770-1740 (γ-lactone, butenolide), 1670 cm^{-1} (C=C). - ^1H NMR: δ = 1.04 (d, J = 7 Hz, 6-Me), 1.05 (s, 8-Me), 1.58, 1.66 (AB, J = 15, A-part ddd, J = 13, 10, 3, B-part ddd, 4, 4, 1 Hz,,5-H_2), 1.80 (ddd, J = 1.5, 1.5, 1.5 Hz, 3-Me), 1.97-2.11 (m, 2 H), 2.45-2.60 (m, 3 H), 2.75-2.90 (m, 2 H), 4.94 (s, br., 8a-H). - ^1H NMR ($CDCl_3/C_6D_6$ 5:1, with spin decoupling): δ = 0.83 (d, J = 7 Hz, 6-Me), 0.85 (s, 8-Me), 1.19, 1.31 (AB, J = 15, A-part ddd, J = 13, 10, 3, B-part ddd, J = 4, 4, 1 Hz, 5-H_2), 1.20, 1.73 (AB, J = 15, A-part dd, J = 12, 6, B-part dd, J = 10, 6 Hz, 4'-H_2),1.60 (ddd, J = 1.5, 1.5, 1.5 Hz, 3-Me), 1.74 (dqd, J = 10, 7, 4 Hz, 6-H), 2.12, 2.37 (AB, J = 20, A-part ddq, J = 13, 4, 1.5, B-part dqd, J = 3, 1.5, 1 Hz, 4-H_2), 2.25, 2.64 (AB, J = 20, A-part dd, J = 10, 6, B-part dd, J = 12, 6 Hz, 3'-H_2), 2.43 (s, br., OH), 4.59 (q, J = 1.5 Hz, 8a-H). - NOED spectrum: ↓ 8a-H → NOE 8-OH, 3'-H, 4'-H, ↓ 8-OH → NOE 8a-H, 3'-H, 8-Me, ↓ 8-Me → NOE 6-H, 8-OH, ↓ 6-Me → NOE 3'-H, 5-H. - ^{13}C NMR: δ = 8.4, 16.0, 17.5 (3 q, 3-, 6-, 8-Me), 21.7, 26.3, 26.8, 30.2 (4 t, C-4, -5, -3', -4'), 38.3 (d, C-6), 78.8 (s, C-8), 83.6 (d, C-8a), 93.4 (s, C-7), 124.2 (s, C-3), 160.5 (s, C-3a), 173.9 (s, C-2), 177.2 (s, C-2'). - MS: m/z (%): 280 (M^+, 9), 262 (10), 237 (9), 220 (34), 219 (28), 202 (26), 177 (37), 125 (69), 112 (100), 110 (38), 55 (60). - $C_{15}H_{20}O_5$ calcd. C 64.27, H 7.19, found C 64.23, H 7.05.

Methyl(5S*,11R*)-2(6,11-dimethyl-1-oxaspiro[4.6]undec-6-en-2-on-8-ylidene)-propionate: (22):

As described for 5 0.36 g (12 mmol) of NaH, 2.84 g (14.5 mmol) of trimethyl phosphonopropionate and 1.25 g (6 mmol) of 15b were stirred for 2 d at room temp., yield 1.02 g (61%) of (E,Z)-22 (1:4). - Recrystallization from PE/ether gave pure (Z)-22, m.p. 124°C. - IR: 1780 (γ-lactone), 1715, 1635 cm^{-1} (C=C-COOR). - ^1H NMR (270 MHz): δ = 0.95 (d, J = 7 Hz, 11-Me), 1.88 (d, J = 1.5 Hz, 6-Me), 1.90 (s, br., Me), 2.95 (mc, 1 H), 3.75 (s, OMe), 6.24 (s, br., 7-H). - ^{13}C NMR: δ = 16.1, 16.4, 21.6 (3 q, 3 Me), 26.0, 29.5, 31.3, 31.9 (4 t, C-3, -4, -9, -10), 38.7 (d, C-11), 91.4 (s, C-5), 128.5 (d, C-7), 144.4, 145.4 (2 s, C-6, -8), =C-COOMe: 124.5 (s), 169.5 (s), 51.4 (q). - MS: m/z (%): 278 (M^+, 10), 247 (10), 236 (10), 219 (15), 207 (100), 164 (62), 106 (50), 90 (53), 63 (70). - $C_{16}H_{22}O_4$ calcd. C 69.04, H 7.97, found C 68.92, H 7.85.

(E)-22: ^1H NMR (from the mother liquor, 90 MHz, CCl_4): δ = 0.95 (d, J = 7 Hz, 11-Me), 1.87 (s, br, 2 Me), 3.70 (s, OMe), 5.30 (s, br., 7-H).

Methyl cis-(5S*,13R*)-6,10,13-trimethyl-1,9-dioxadispiro[4.3.2.2]tridec-6-en-2--one-10-carboxylate (23):

As described for 6 0.28 g (1.0 mmol) of (Z)-22 and 0.22 g (1.1 mmol) of mCPBA were stirred for 2 d at room temp. - FC (PE/ether 1:3) of the crude product (0.28 g, (95%) gave as 1. fraction 90 mg of 23, 1. isomer, oily. - IR: 1785 (γ-lactone), 1735 (COOR) cm^{-1}. - ^1H NMR: δ = 0.96 (d, J = 7 Hz, 13-Me), 1.52 (s, 10-Me), 1.84 (d, J = 1.5 Hz, 6-Me), 3.80 (s, OMe), 5.39 (s, br., 7-H). - ^{13}C NMR: δ = 17.2, 17.6, 23.2 (3 q, 6-, 10-, 13-Me), 28.2, 29.2, 29.8, 32.5 (4 t, C-3, -4, -11, -12), 38.8 (d, C-13), 64.7, 65.7 (2 s, C-9,-10), 91.4 (s, C-5), 125.1 (d, C-7), 148.3 (s, C-6), 176.1 (s, C-2), COOMe: 170.6 (s, 52.3 (q). -
0.18 g of 23, 2. isomer, oily, was isolated as 2. fraction. - ^1H NMR: δ = 0.98 (d, J = 7 Hz, 13-Me), 1.53 (s, 10-Me), 1.84 (d, J = 1.5 Hz, 6-Me), 3.79 (s, OMe), 5.43 (s, br., 7-H). - ^{13}C NMR: δ = 16.4, 17.1, 21.7 (3 q, 6-, 10-, 13-Me), 26.5, 27.6, 29.4, 29.9 (4 t, C-3, -4, -11, -12), 38.8 (d, C-13), 64.1, 64.9 (2 s, C-9, -10), 90.8 (s, C-5), 128.1 (d, C-7), 145.8 (s, C-6), 176.2 (s, C-2), COOMe: 170.8 (s), 52.4 (q). - $C_{16}H_{22}O_5$ calcd. C 65.29, H 7.53, found C 65.15, H 7.42.

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