64. First Total Synthesis of Enantiomerically Pure (−)-Silphiperfol-6-en-5-on[1])

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The angular triquinane (−)-silphiperfol-6-en-5-on ((−)-**14**) has been synthesized for the first time in enantiomerically pure form. A highly efficient triplet-sensitized photoreaction, the oxadi-π-methane rearrangement of the complex β,γ-enone (+)-**6** to (−)-**7**, constitutes the key step. The known starting material, (1*R*,7a*R*)-3,6,7,7a-tetrahydro-1-hydroxy-7a-methyl-1*H*-inden-5(2*H*)-one ((−)-**2**), is readily accessible in > 97% enantiomeric purity. This new approach should enable access also to other angularly fused triquinanes of the silphinene type and related structures.

Introduction. – We have recently presented a novel approach [2] which extends the synthetic tricyclooctanone strategy for diquinanes [3] and provides a ready access to both linearly[3]) and angularly annulated triquinanes. We now describe as a first example the total synthesis of (−)-silphiperfol-6-en-5-one (**14**), a representative of the angular triquinanes.

The title compound has been isolated by *Bohlmann et al.* [4] from the stems of *Espeletiopsis guacharaca*. The biogenesis of the silphinenes, in general, has been proposed to proceed *via* caryophyllene [5]. The absolute configuration of (−)-**14** has subsequently been established by *Paquette et al.* in a synthesis of enantiomerically enriched material[4]) starting from (+)-*R*-pulegon [6]. Our synthesis of natural (−)-**14** confirms the assignment in a sequence which affords for the first time the target material in > 97% enantiomerically pure form. In this context, it should be noted that an apparent discrepancy of absolute configuration between the biosynthesis proposal [5] and the silphinene configuration ascertained on the basis of synthesis is due to an erroneous drawing which in [5] should be corrected to correspond to the natural enantiomer of the intermediate *trans*-caryophyllene.

Results and Discussion. – The key step of our synthesis involves the highly efficient triplet-sensitized oxadi-π-methane rearrangement of a structurally rather complex β,γ-

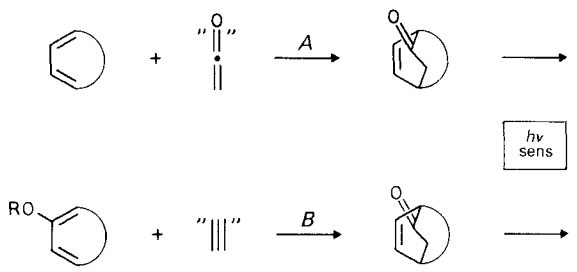
[1]) For a preliminary communication of this work, see [1a,b] [2].

[2]) Part of the dissertation of *W.H.*, *Max-Planck*-Institut für Strahlenchemie/Ruhr-Universität Bochum, 1986; present address: *Bayer AG*, D-5600 Wuppertal.

[3]) On this occasion, we should like to add a correction. A recently performed X-ray analysis has revealed that the five-membered rings of the linearly annulated triquinane structure shown in [2] (compound **9** in [2]) are not *cis, anti, cis*-fused, as assigned previously by NMR, but they are *cis, syn, cis*-fused. This finding demands at the same time that the etheno and oxoethano bridges of the β,γ-enone **8** shown in [2] must be interchanged as a consequence of the well established mechanism of oxadi-π-methane rearrangements.

[4]) For the synthesis of the parent deoxo product silphiperfol-6-ene in enantiomerically enriched and in racemic form, see [6] and [7], respectively.

Scheme 1. *Topochemically Complementary Methods for the Generation of the Photochemical Substrates, the Cyclic β,γ-Enones, from 1,3-Dienes Using Ketene (Path A) or Acetylene (Path B) Equivalents.* The latter path includes consecutive addition and enol ether→ketone transformation. Preferential β-addition of the dienophile is presumed for both cases.



enone. In contrast to our earlier preparations of β,γ-enones where 1,3-dienes were reacted with ketene equivalents (*Path A* in *Scheme 1*), the enone is now assembled by addition of an acetylene equivalent to a silyloxy-substituted diene (*Path B* in *Scheme 1*). The two variants are topochemically complementary with respect to the resulting spatial arrangement of the etheno and oxoethano bridges in the β,γ-enones, provided that similar stereoelectronic factors steer the additions.

The synthesis starts from the (1*R*,7a*R*)-methoxyethoxymethyl(MEM) ether (−)-**3** of (1*R*,7a*R*)-3,6,7,7a-tetrahydro-1-hydroxy-7a-methyl-1*H*-inden-5(2*H*)-one ((−)-**2**) [8] which in turn is derived from (−)-**1**[5]). Kinetic deprotonation of (−)-**3** gave, as expected [10], exclusively the 5-en-5-olate which was trapped with Me_3SiCl following the *Corey* method [11]. For the subsequent *Diels-Alder* addition, maleic anhydride was chosen as acetylene equivalent and was thermally reacted with **4**. This addition is efficiently directed by the angular Me-C(7a) to occur exclusively on the β-side of **4**, and it follows the common *endo* mode of [4 + 2] processes (→(−)-**5**). The adduct (−)-**5** was subjected to electrolysis without further purification [12]. Under the conditions applied, (−)-**5** was hydrolyzed *in situ* to the corresponding vicinal diacid (monitored by NMR) which decarboxylated electrolytically to (+)-**6** (overall yield: 60%)[6]). The electrolytic method proved superior to the more common decarboxylation procedures in which $Pb(OAc)_4$ or Ni complexes are employed. The subsequent photochemical rearrangement (1% acetone solution, λ(irr.) 300 nm) of (+)-**6** afforded (−)-**7** in a remarkably high yield of 70%. GLC analysis revealed that the crude reaction mixture contained *ca.* 90% of oxadi-π-methane product (−)-**7** besides 5% of a product (−)-**8** which is formed by a competing 1,3-acyl shift due to residual direct light absorption by (+)-**6**[7]). The crucial success of step (+)-**6**→(−)-**7** is in accord with earlier experience with structurally simpler enones. It could not have been predicted with confidence, however, since bridgehead-substituted β,γ-enones are occasionally found to be photochemically unreactive [1b,c] [3].

The conversion to the final product (−)-**14** demanded further transformations at two sites of (−)-**7**: firstly, the reductive cleavage of the cyclopropyl ketone, methylation at

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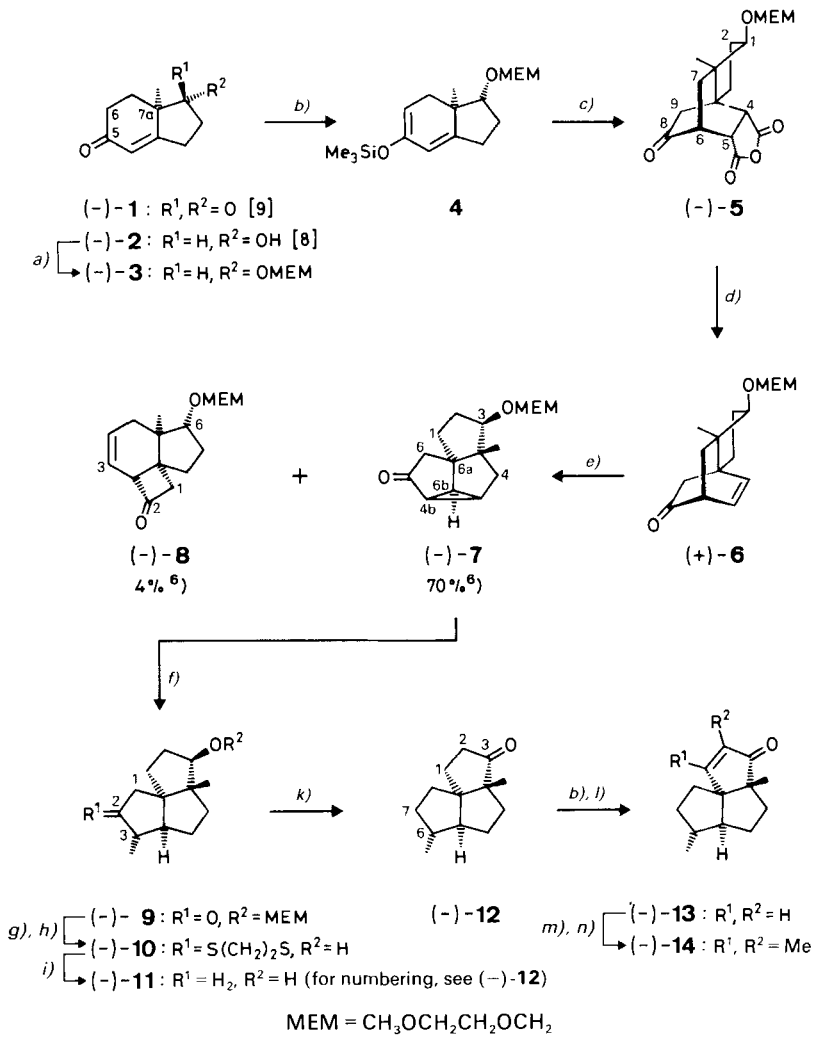
[5]) Both enantiomers **1** are accessible in high yields and purities (> 97% e.e.) *via* asymmetric prolin-catalyzed *Robinson* annulation of 2-methylcyclopentane-1,3-dione with methyl vinyl ketone [9].

[6]) Yields refer to chromatographically purified compounds.

[7]) For the photochemical 1,3-acyl shift of β,γ-enones, see [13].

Scheme 2. *Synthesis of (−)-Silphiperfol-6-en-5-one* ((−)-**14**). *a*) Methoxyethoxymethyl chloride, Et(i-Pr)$_2$N, CH_2Cl_2, r.t.; *b*) Lithium diisopropylamide (LDA), Me_3SiCl, −78°; *c*) Maleic anhydride, no solvent, r.t., 4 h; *d*) 90% aq. pyridine, Et_3N, 4-(*tert*-butyl)catechol, electrolysis (carbon electrodes at 200-V potential); *e*) 1% Ar-degassed acetone soln., λ = 300 nm (*Rayonet* apparatus with *RPR*-3000-Å lamps), r.t.; *f*) 1) Li, *t*-BuOH (1 equiv.), Me_3SiCl, (i-Pr)$_2$NH, THF, r.t., 6 h; 2) $PhCH_2(Me)_3NF$, molecular sieves, THF, MeI, 0°, 0.5 h; *g*) $TiCl_4$, CH_2Cl_2, 0°, 0.5 h; *h*) $Mg(SO_3CF_3)_2$ (10 equiv.), 1,2-ethanedithiol, CH_2Cl_2, r.t., 3 h; *i*) $TiCl_4$, $LiAlH_4$, THF, r.t., 24 h; *k*) $H_2Cr_2O_7$, Et_2O, 0°, 10 min; *l*) DDQ, *N,O*-bis (trimethylsilyl)-2,2,2-trifluoroacetamide, benzene, r.t., 48 h; *m*) Me_2CuLi, Et_2O/THF 4:1, 0°; MeI, HMPA; *n*) 1) conditions of *Footnote b*; 2) conditions of *Footnote l*, but at 45°.



C(4b) utilizing the reductively and regiospecifically formed enolate, and removal of the keto group; secondly, oxidation of the saturated 3-hydroxy function to the enone and vicinal dimethylation of this group. The three-membered ring of (−)-**7** was most efficiently cleaved with Li in THF in the presence of Me_3SiCl and (i-Pr)$_2$NH, whereby the

intermediate 2-en-2-olate (for numbering, see **9**) was trapped as the silyl-ether derivative. To our knowledge, this method as employed for the reductive silylation of **7** is novel, and its generality has yet to be demonstrated. The reaction conditions for this step could be directly adopted from the known procedure for the reductive silylation of benzene [14]. In the following step, the Me_3SiO group was cleaved with fluoride [15], and the liberated enolate was α-methylated with MeI predominantly at C(3) ($3\alpha/3\beta$-methyl in the crude reaction mixture, 12:1; (−)-**7**→(−)-**9**, 45% yield). Analogous attempts at reductive monomethylation in NH_3 were unsuccessful, and C(1)- and C(3)-polymethylated products resulted instead. It is also interesting to note that consecutive *Birch* reduction of (−)-**7** and methylation of the enolate, which is formed with NaH in THF, gave exclusively the rather unexpected 1α-methyl compound.

At this stage of the synthesis, the C(2) keto group, which had served to steer the individual steps, could be removed *via* the thioacetal. Thus, (−)-**10** was cleanly formed with magnesium triflate and 1,2-ethanedithiol, after the cleavage of the MEM group of (−)-**9** with $TiCl_4$, in an overall yield of 80%. Thioacetalization *via* this method is known [16] to be successful also with sterically hindered ketones. The subsequent removal of the dithia bridge was unsatisfactory when the standard reduction procedure using *Raney*-Ni was employed[8]). A 63% yield of (−)-**11** was achieved, however, with the *Mukaiyama* reagent ($TiCl_4/LiAlH_4$) [18]. As side products, 15–18% of the 6,7- and 7,8-unsaturated isomers of (−)-**11** were formed, which were hydrogenated (10% Pd/C) and contributed to the aforementioned yield of (−)-**11**, in addition to 11% of the C(6) epimer. The alcohol (−)-**11** was then oxidized with chromic acid, adopting the procedure B of [19], to afford (−)-**12** in 84% yield. The trimethylsilyl enol ether of (−)-**12**, cleanly generated by the method already employed to prepare **4**, was dehydrogenated with 4,5-dichloro-3,6-dioxo-1,4-cyclohexadiene-1,2-dicarbonitrile (DDQ) in the presence of *N,O*-bis(trimethylsilyl)-2,2,2-trifluoroacetamide ((−)-**12**→(−)-**13**, 70% yield). The target compound (−)-silphiperfol-6-en-5-one ((−)-**14**; skeletal numbering of (−)-**14** adopted from [4]) resulted in pure form after consecutive vicinal dimethylation (lithium dimethylcuprate; MeI in hexamethylphosphoric triamide (HMPA)) [20] and reformation of the enone moiety by DDQ oxidation at 45° from (−)-**13** (52% overall yield). The spectroscopic analysis of (−)-**14** (IR, MS, ^{1}H- and ^{13}C-NMR) as well as the specific rotation $[\alpha]_D^{23} = -39.5°$ ($CHCl_3$, $c = 0.34$) fully agree with the data reported for the natural material (*cf.* [4]: $[\alpha]_D^{24} = -40°$ ($CHCl_3$, $c = 1.3$)) [4].

In conclusion, we should like to note that the present approach, in view of the pattern of substituents and functional groups in the key intermediate (−)-**7**, should enable access also to other silphinene-type triquinanes and related natural products[9]).

Partial financial support of these investigations by the *Deutsche Forschungsgemeinschaft* is gratefully acknowledged.

[8]) Similar problems were encountered in [17].

[9]) For reviews, see [21a]. For the isolation of a related triquinane, see [21b]. First isolation of structurally related tetraquinanes: [21c].

Experimental Part

General. The solvents were purified using standard procedures. All reactions were run under Ar. Column chromatography and flash chromatography: on silica gel (*Merck*; 0.063–0.2 mm). Prep. TLC: 2-mm silica plates (*Merck*). M.p.: *Kofler* hot plate; uncorrected. $[\alpha]_D$: at 23° in $CHCl_3$; exper. error ±5%. UV spectra (EtOH): *Cary-17* spectrophotometer; λ max (ε) in nm. IR spectra: in $CHCl_3$, unless stated otherwise; *Perkin-Elmer-298* instrument; in cm^{-1}. ^{13}C-NMR (100.6 MHz) and ^{1}H-NMR spectra: in $CDCl_3$, unless stated otherwise; *Bruker-AM-400* instrument; chemical shifts in ppm rel. to TMS (= 0 ppm) and coupling constants J in Hz. MS (in m/z): *Varian MAT CH5* instrument at 70 eV. GLC: *Carlo-Erba-4100* instrument equipped with a flame-ionization detector coupled to a *Spectra Physics Autolab System I* integrator; *OV 101* glass capillary columns of 20 and 35 m length; N_2 as carrier gas. The elemental analyses were performed by *Dornis* and *Kolbe*, Mülheim a.d. Ruhr.

(−)-(1R,7aR)-3,6,7,7a-Tetrahydro-1-(methoxyethoxymethyl)-7a-methyl-1H-inden-5(2H)-one ((−)-**3**). To a soln. of (−)-**2** [8] (10 g, 0.06 mol) in CH_2Cl_2 (110 ml) and Et(i-Pr)$_2$N (15 ml, 0.09 mol), methoxyethoxymethyl chloride (10.7 ml, 0.09 mol) was added dropwise under stirring at 0° and the reaction continued at r.t. (21 h). Then, the solvent was evaporated, brine added to the residue, and the mixture repeatedly extracted with Et_2O. The combined org. layers were dried (Na_2SO_4) and evaporated. The residue was flash chromatographed (silica gel, 20-fold; hexane/Et_2O 1:1): pure (−)-**3** (12.18 g, 79.6%; > 98% purity). $[\alpha]_D = -32.2°$ ($c = 0.58$). IR: 1648. ^{1}H-NMR: 1.13 (*s*, 3 H); *ca.* 1.74–1.86 (*m*, 2 H); *ca.* 2.06–2.12 (*m*, 1 H); *ca.* 2.13–2.20 (*m*, 1 H); *ca.* 2.30–2.42 (*m*, 2 H); *ca.* 2.43–2.54 (*m*, 1 H); *ca.* 2.63–2.74 (*m*, 1 H); 3.37 (*s*, 3 H); *ca.* 3.52–3.58 (*m*, 2 H); *ca.* 3.67–3.76 (*m*, 3 H); 4.73 (*d*, $J = 8.5$, 1 H); 4.77 (*d*, $J = 8.5$, 1 H); 5.75 (*dd*, $J = 2.3, 2.3$, 1 H). ^{13}C-NMR (67.8 MHz): 198.75, 174.10, 44.89 (3 *s*); 123.28, 85.39 (2 *d*); 95.18, 71.78, 67.07, 34.57, 33.29, 26.91, 26.48 (7 *t*); 58.93, 15.91 (2 *q*). MS: 254 ($M^{+\cdot}$, $C_{14}H_{22}O_4$), 178, 164, 149, 122, 105, 89, 59 (100).

(1R,7aR)-2,3,7,7a-Tetrahydro-1-(methoxyethoxymethoxy)-7a-methyl-5-(trimethylsilyloxy)-1H-inden (**4**) *and (−)-(1R,3aR,4R,5R,6R,7aR)-2,3,3a,4,5,6,7,7a-Octahydro-1-(methoxyethoxymethoxy)-7a-methyl-8-oxo-1H-3a,6-ethanoindene-4,5-dicarboxylic Anhydride* ((−)-**5**). a) *Trimethylsilyloxy Derivative* **4**. (i-Pr)$_2$NH (11.35 ml, 80 mmol) in THF (200 ml) was cooled to −78° and BuLi (59 mmol) added. After warming to *ca.* −40°, it was cooled again to −78°. Directly after addition of freshly distilled Me_3SiCl (45.4 ml, 360 mmol), (−)-**3** (9.3 g, 36.6 mmol) in 70 ml of THF was added dropwise. After 5 min, Et_3N (50 ml, 360 mmol) was added and then the cold mixture directly poured into vigorously stirred petroleum ether (b.p. 40–60°)/sat. aq. $NaHCO_3$ soln. After repeated extractions with more petroleum ether, the combined org. layer was washed with H_2O, the pH of the aq. layer adjusted to 4–5 with citric acid, and the procedure repeated until the pH remained constant. The org. extract was consecutively washed with $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated. The remaining **4**, characterized as crude material by ^{1}H-NMR and IR (> 92% purity by GLC), is quite labile and was directly used in the subsequent step without purification.

b) Diels-Alder *Addition* **4**→(−)-**5**. The diene **4** (see *a*) was dried at 10^{-2} Torr for 2 h before freshly sublimed and finely powdered maleic anhydride (5.37 g, 54.7 mmol) was added to it. The mixture was stirred at r.t. for 4 h, then the volatile components were removed at 10^{-2} Torr at r.t. overnight. The residue in Et_2O was filtered on silica gel (130 g), the silica gel additionally eluted with $CHCl_3$, and the combined fractions were evaporated. The remaining light-yellow solid was suspended in Et_2O and filtered and the residue washed with 5–10 ml of cold acetone to afford white, crystalline (−)-**5** (7.17 g). The filtrate was evaporated and the residue dissolved in 10 ml of Et_2O. While storing this soln. at −20°, another fraction of crystalline (−)-**5** (0.512 g) precipitated (total yield, 59.6%). M.p. 108°. $[\alpha]_D = -46.8°$ ($c = 0.53$). IR: 1775, 1730. ^{1}H-NMR: 0.95 (*s*, 3 H); *ca.* 1.63–1.90 (*m*, 4 H); 2.05 (*d*, $J = 19.5$, 1 H); *ca.* 2.30–2.41 (*m*, 1 H); *ca.* 2.43–2.51 (*m*, 1 H); 2.50 (*dd*, $J = 2.5, 19.5$, 1 H); 2.91 (*ddd*, $J = 2.1, 3.9, 3.9$, 1 H); 3.24 (*dd*, $J = 2.5, 10$, 1 H); 3.36 (*s*, 3 H); 3.42 (*dd*, $J = 3,9, 10$, 1 H); *ca.* 3.48–3.57 (*m*, 2 H); *ca.* 3.59–3.65 (*m*, 1 H); *ca.* 3.67–3.73 (*m*, 1 H); 4.05 (*dd*, $J = 7.4, 8.9$, 1 H); 4.68 (*d*, $J = 7$, 1 H); 4.71 (*d*, $J = 7$, 1 H). ^{13}C-NMR: 209.49, 171.63, 170.80, 48.43, 44.07 (5 *s*); 83.34, 44.28, 43.42, 43.26 (4 *d*); 94.73, 71.49, 66.86, 43.83, 37.70, 28.40, 26.10 (7 *t*); 58.87, 17.66 (2 *q*). MS: 352 ($M^{+\cdot}$, $C_{18}H_{24}O_7$), 247, 219, 175, 133, 117, 89 (100), 59. Anal. calc. for $C_{18}H_{24}O_7$: C 61.35, H 6.87; found: C 61.40, H 6.89.

(+)-(1R,3aR,6R,7aR)-2,3,3a,6,7,7a-Hexahydro-1-(methoxyethoxymethoxy)-7a-methyl-1H-3a,6-ethanoinden-8-one ((+)-**6**). To a pyridine (110 ml) soln. of (−)-**5** (1 g, 2.85 mmol), Et_3N (0.8 ml), tridistilled H_2O (8.5 ml), and 4-(*tert*-butyl)catechol (22 mg) were added. This mixture was electrolyzed with carbon electrodes (size 2 × 4 cm, at 2 cm distance) at 200-V potential for 20 h. The temp. of the reaction media was maintained at 3–5°. An initial current of 80 mA was typically measured. For workup, the pyridine was largely evaporated, then Et_2O and H_2O were added to the concentrate, and the aq. layer was adjusted to pH 1–2 by dropwise adding 30% HCl soln. Repeated extractions with Et_2O followed. The combined org. layers were then consecutively washed with $NaHCO_3$ soln. and brine prior to drying (Na_2SO_4). Evaporation of the org. solvent afforded a red-brown oil which was

chromatographed on silica gel (50-fold; hexane/Et_2O 1:1): pure (+)-**6** (0.448 g, 56.3%; 99.3% purity). $[\alpha]_D$ = +272.8° (0.4). UV: 297 (118). IR: 1715, 1610. ^{1}H-NMR (270 MHz): 0.97 (*s*, 3 H); 1.62 (*dd*, *J* = 3.3, 13, 1 H); *ca.* 1.68–1.81 (*m*, 3 H); 1.78 (*dd*, *J* = 2.6, 13, 1H); 2.23 (*d*, *J* = 18, 1 H); 2.98 (*dddd*, *J* = 2.6, 2.6, 3.3, 5.2, 1 H); 3.33 (*s*, 3 H); *ca.* 3.46–3.53 (*m*, 2 H); *ca.* 3.59–3.66 (*m*, 2 H); 3.76 (*dd*, *J* = 9.5, 7.6, 1 H); 4.62 (*d*, *J* = 7, 1 H); 4.66 (*d*, *J* = 7, 1 H); *ca.* 6.18–6.25 (*m*, 2 H). ^{13}C-NMR: 213.85, 49.58, 46.92 (3 *s*); 143.50, 129.50, 85.43, 50.50, (4 *d*); 94.99, 71.66, 66.84, 42.57, 39.16, 29.14, 28.41 (7 *t*); 58.96, 17.43 (2 *q*). MS: 280 (M^+, $C_{16}H_{24}O_4$), 204, 175, 144, 128, 105, 89 (100), 59.

*(−)-(3*R*,3a*R*,6a*R*,6b*S*)-2,3,3a,4,4a,4b,6,6b-Octahydro-3-(methoxyethoxymethoxy)-3a-methylcyclopenta[*c*]-cyclopropa[*gh*]pentalen-5(1*H*)-one* ((−)-**7**). A soln. of (+)-**6** (0.575 g, 2.05 mmol) in acetone (80 ml) was purged with Ar and irradiated in a H_2O-cooled quartz vessel placed in a *Rayonet RPR-208* photoreactor (*RUL*-3000-Å lamps). After 3.5 h, 95% of the (+)-**6** were converted into (−)-**7** (90% by GLC) and (−)-**8** (5% by GLC). The acetone was distilled off. Chromatography of the residue (silica gel, 100-fold; pentane/Et_2O 1:1) afforded (−)-**7** (0.404 g, 70.3%; 99.8% purity). $[\alpha]_D$ = −42.7° (*c* = 0.54). UV: 284 (166). IR: 1715. ^{1}H-NMR (270 MHz): 0.81 (*s*, 3 H); *ca.* 1.35–1.42 (*m*, 1 H); *ca.* 1.52–1.98 (*m*, 5 H); *ca.* 2.10–2.33 (*m*, 4 H); *ca.* 2.38–2.44 (*m*, 1 H); 3.38 (*s*, 3 H); *ca.* 3.50–3.57 (*m*, 2 H); *ca.* 3.60–3.73 (*m*, 2 H); 4.20 (*dd*, *J* = 8.7, 8.7, 1 H); 4.70 (*d*, *J* = 7, 1 H); 4.75 (*d*, *J* = 7, 1 H). ^{13}C-NMR (75.5 MHz): 213.70, 60.33, 56.12 (3 *s*); 83.58, 43.57, 38.33, 28.24 (4 *d*); 95.40, 71.76, 66.89, 48.36, 36.45, 28.41, 28.35 (7 *t*); 58.91, 13.73 (2 *q*). MS: 280 (M^+, $C_{16}H_{24}O_4$), 224, 204, 190, 174, 149, 105, 89 (100), 59. Anal. calc. for $C_{16}H_{24}O_4$): C 68.55, H 8.63; found: C 68.60, H 8.58.

With the initial fractions of the chromatography were eluted first (+)-**6** (21 mg, 3.5%), then (−)-**8** (23 mg, 4%; 99% purity).

*(−)-(2a*R*,5a*R*,6*R*)-2a,5,5a,6,7,8-Hexahydro-6-(methoxyethoxymethoxy)-5a-methylcyclobuta[*d*]inden-2(1*H*)-on* ((−)-**8**). $[\alpha]_D$ = −305.9° (*c* = 0.37). UV: 296 (261). IR: 1775, 1605. ^{1}H-NMR: 0.88 (*s*, 3 H); 1.57–1.66, 1.7–1.78 (*m*, each 1 H); 1.83 (*dddd*, *J* = 2, 3, 3, 18.4, 1 H); 2.0–2.12 (*m*, 2 H); 2.26 (*dddd*, *J* = 1.5, 1.5, 5.9, 18.4, 1 H); 2,63 (*dd*, *J* = 5.4, 17.7, 1 H); 3.04 (*dd*, *J* = 2.8, 17.7, 1 H); 3.15–3.21 (*m*, 1 H); 3.37 (*s*, 3 H); 3.49–3.54 (*m*, 2 H); *ca.* 3.64 (*m*, 2 H); 3.81 (*dd*, *J* = 7.7, 8.8, 1 H); 4.64 (*d*, *J* = 7, 1 H); 4.71 (*d*, *J* = 7, 1 H); 5.51–5.56, 5.68–5.74 (*m*, each 1 H). ^{13}C-NMR: 205.51, 41.11, 39.27 (3 *s*); 126.35, 119.94, 80.25, 65.35 (4 *d*); 95.14, 71.59, 66.68, 50.64, 33.81, 30.20, 26.40 (7 *t*); 58.87, 17.07 (2 *q*). MS: 280 (M^+, $C_{16}H_{24}O_4$), 204, 162, 147, 130, 118, 105, 89 (100), 59.

*(−)-(3*S*,3a*S*,5a*R*,6*R*,8a*R*)-3,3a,4,5,5a,6,7,8-Octahydro-6-(methoxyethoxymethyl)-3,5a-dimethylcyclopenta[*c*]pentalen-2(1*H*)-one* ((−)-**9**). Into a soln. of (−)-**7** (0.205 g, 0.73 mmol) in THF (15 ml), containing a few glass splinters, were added by syringe consecutively *t*-BuOH (62 µl, 0.66 mmol) and 0.24 ml of the supernatant of a centrifuged 1:1 mixture $Me_3SiCl/(i\text{-}Pr)_2NH$. After Li (21 mg, 3 mmol) was added, the suspension was vigorously stirred at r.t. until all the metal was consumed (6 h). The subsequent workup followed the procedure described for the preparation of **4**. The resultant trimethylsilyl 2-en-2-ol ether was characterized as crude material by ^{1}H-NMR and IR and directly used in the following methylation step.

To benzyl(trimethyl)ammonium fluoride (0.175 g, 0.93 mmol; dried at 50° for 24 h at 10^{-2} Torr) in a three-necked flask, activated molecular sieves (1.5 g, 4 Å) were added, the vessel was cooled to −196°, and THF (6 ml, freshly distilled over $LiAlH_4$) condensed into the flask at reduced pressure (10^{-2} Torr). The suspension was then vigorously stirred at r.t. overnight. After cooling to 0°, a soln. of the trimethylsilyl 2-en-2-ol ether in MeI (3 ml, distilled over P_2O_5) was added dropwise and the mixture stirred for 30 min prior to pouring it into Et_2O/dil. NaCl soln. The aq. layer was weakly acidified with NH_4Cl and repeatedly extracted with Et_2O. The combined org. extracts were dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed on silica gel (110-fold; hexane/Et_2O 4:1 to 1:1). With the first fractions, a 6:1 mixture (−)-**9**/C(3) epimer was eluted (96.1 mg, 47.6% corrected yield, 95% purity). With the further fractions, unreacted (+)-**6** (14 mg) was recovered. For anal. purposes, only the mixture (−)-**9**/C(3) epimer was again chromatographed on silica gel (200-fold, hexane/Et_2O 1:1) using a *Multibore* column to obtain pure (−)-**9**. $[\alpha]_D$ = −40.5° (*c* = 0.34). IR: 1730. ^{1}H-NMR: 0.92 (*s*, 3 H); 1.06 (*d*, *J* = 7, 3 H); *ca.* 1.44–1.52 (*m*, 1 H); *ca.* 1.56–1.69 (*m*, 4 H); *ca.* 1.71–1.80 (*m*, 2 H); *ca.* 1.82–1.99 (*m*, 3 H); 2.09 (*d*, *J* = 18.5, 1 H); 2.64 (*dd*, *J* = 1.1, 18.5, 1 H); 3.37 (*s*, 3 H); *ca.* 3.51–3.54 (*m*, 2 H); *ca.* 3.61–3.73 (*m*, 3 H); 4.66 (*d*, *J* = 7, 1 H); 4.73 (*d*, *J* = 7, 1 H). ^{13}C-NMR: 221.54, 55.92, 53.79 (3 *s*); 86.67, 58.55, 48.44 (3 *d*); 94.51, 71.78, 66.85, 47,94, 40.07, 38.77, 29.74, 29.07 (8 *t*); 59.02, 20.64, 15.06 (3 *q*). MS: 296 (M^+, $C_{17}H_{28}O_4$), 239, 206, 191, 149, 119, 105, 89 (100), 59.

*(−)-(3*S*,3a*S*,5a*R*,6*R*,8a*R*)-3,3a,4,5,5a,6,7,8-Octahydro-6-hydroxy-3,5a-dimethylcyclopenta[*c*]pentalen-2(1*H*)-one Ethylen Dithioacetal* ((−)-**10**). a) *Cleavage of the OMEM Group of* (−)-**9**. To a soln. of $TiCl_4$ (0.77 ml, 7.04 mmol; freshly distilled) in CH_2Cl_2 (10 ml; distilled over P_2O_5) at 0° was added dropwise (−)-**9** (0.208 g, 0.7 mmol; 6:1 mixture of C(3) epimers) in CH_2Cl_2 (5 ml). The mixture was stirred for 20 min, before H_2O (10 ml) was added. The slurry was subsequently poured into sat. $NaHCO_3$ soln. and repeatedly extracted with Et_2O. The combined org. extracts were dried (Na_2SO_4) and evaporated. Chromatography of the residual oil (silica gel,

50-fold; hexane/Et_2O 3:1) afforded a 6:1 mixture of 6β-hydroxycyclopenta[*c*]pentalen-2(1*H*)-ones (epimers at C(3); assignment of structure by IR, MS, ^{1}H- and ^{13}C-NMR).

b) *Thioacetalization.* Magnesium trifluoromethanesulfonate [16] (0.865 g, 2.68 mmol) and 1,2-ethanedithiol (0.18 ml, 2.16 mmol) were added to the 6β-hydroxy ketones (6:1, see *a*); 0.224 g, 1.08 mmol). The mixture was stirred at r.t. for 48 h before hexane/Et_2O 1:1 (80 ml) and sat. $NaHCO_3$ soln. were added consecutively. The separated aq. layer was repeatedly extracted with $CHCl_3$, the combined org. extract dried (Na_2SO_4) and evaporated. Chromatography of the residual oil (silica gel, 100-fold; hexane/Et_2O 4:1) afforded (−)-**10**/C(3) epimer (6:1; 0.181 g, 92.4%; > 95% purity). For anal. purposes only, the epimeric mixture was again chromatographed (conditions as before) to yield the pure, white, crystalline (−)-**10**. M.p. 71°. $[\alpha]_D = -42.0°$ (*c* = 0.33). IR: 3610, 3560–3280. ^{1}H-NMR: 0.89 (*s*, 3 H); 1.06 (*d*, *J* = 6.1, 3 H); *ca.* 1.27–1.33 (*m*, 1 H); *ca.* 1.36–1.45 (*m*, 2 H); *ca.* 1.49–1.59 (*m*, 1 H); *ca.* 1.64–1.91 (*m*, 7 H); 2.04 (*d*, *J* = 13.5, 1 H); 2.39 (*d*, *J* = 13.5, 1 H); *ca.* 3.19–3.25 (*m*, 4 H); 3.79 (*dd*, *J* = 6, 7, 1 H). ^{13}C-NMR: 76.51, 59.02, 55.35 (3 *s*); 78.50, 61.90, 52.95 (3 *d*); 54.70, 40.07, 39.22, 39.06, 37.52, 33.35, 28.14 (7 *t*); 16.59, 13.61 (2 *q*). MS: 284 (M^+, $C_{15}H_{24}OS_2$), 266, 256 (100), 223, 173, 154, 105, 91, 79, 61.

*(−)-(3*R*,3a*R*,5a*S*,6*R*,8a*S*)-Perhydro-3a,6-dimethylcyclopenta[c]pentalen-3-ol* ((−)-**11**). THF (20 ml) was condensed onto $LiAlH_4$ (0.375 g, 9.91 mmol) at −196°. After warming to r.t., $TiCl_4$ (0.28 ml, 2.55 mmol, freshly distilled) was added dropwise and the mixture stirred for 1 h. The resultant dark soln. of the reducing reagent was then added by syringe into a second flask containing (−)-**10**/C(3) epimer (6:1; 0.282 g, 0.99 mmol). This mixture, while stirring, was warmed to 85° for 3 h, then cooled to 0° before dropwise adding it to a sat. $NaHCO_3$ soln. After repeated extractions with Et_2O, the combined org. portions were dried (Na_2SO_4) and evaporated. The residual oil was chromatographically purified (silica gel, 100-fold; hexane/Et_2O 6:1). A mixture (−)-**11**/C(6) epimer was obtained, contaminated, however, with 15–18% of the corresponding 6, 7- and 7,8-unsaturated derivatives. The mixture was taken up in EtOH (20 ml) and hydrogenated in presence of 30 mg 10% Pd/C (12 h). After removal of the catalyst by filtration through *Celite*, the EtOH was evaporated to give (−)-**11**/C(6) epimer 6:1 (0.143 g, 74%; > 98% purity). Quantitative separation of the epimers was achieved by HPLC on a C_{18} *Nucleosil 7* column ($MeOH/H_2O$ 85:15, rate 1 ml/min, 40 bar). Anal. data of the white crystalline (−)-**11**. M.p. 27° $[\alpha]_D = -49.5°$ (*c* = 0.94). ^{1}H-NMR: 0.90 (*m*, 3 H); 0.94 (*d*, *J* = 6, 3 H); *ca.* 1.16–1.26 (*m*, 2 H); *ca.* 1.31–1.58 (*m*, 7 H); *ca.* 1.59–1.76 (*m*, 5 H); *ca.* 1.77–1.86 (*m*, 1 H); 3.78 (*dd*, *J* = 5, 5, 1 H). ^{13}C-NMR: 62.13, 54.65 (2 *s*); 80.15, 62.92, 41.74 (3 *d*); 39.72, 39.35, 36.19, 36.13, 32.21, 30.23 (6 *t*); 20.33, 17.39 (2 *q*). IR: 3600, 3540–3300. MS: 194 (M^+, $C_{13}H_{22}O$), 176, 150, 135, (100), 121, 107, 95, 81, 67. Anal. calc. for $C_{13}H_{22}O$: C 80.35, H 11.41; found: C 80.28, H 11.38.

*(−)-(3a*R*,5a*S*,6*R*,8a*S*)-2,3a,4,5,5a,6,7,8-Octahydro-3a,6-dimethylcyclopenta[c]pentalen-3(1*H*)-one* ((−)-**12**). At 0° 4 ml of a cold (0°) chromic-acid soln. [19] were dropped into a stirred soln. of (−)-**11** (0.151 g, 0.78 mmol) in Et_2O (25 ml). A 2nd portion of the chromic-acid reagent (3.8 ml) was added 5 min later, and the reaction stirred for additional 5 min. Separation of the org. layer and extraction of the aq. phase with Et_2O followed. The combined org. portions were washed consecutively with sat. $NaHCO_3$ soln. and brine prior to drying (Na_2SO_4) and evaporation. Chromatography of the residue (silica gel, 100-fold; hexane/Et_2O 30:1) gave (−)-**12** (0.144 g, 96.5%; 99.5% purity). $[\alpha]_D = -253.6°$ (*c* = 0.9). IR: 1730. ^{1}H-NMR: *ca.* 0.79–0.89 (*m*, 1 H); 0.89 (*s*, 3 H); 1.00 (*d*, *J* = 6.5, 3 H); *ca.* 1.22–1.50 (*m*, 5 H); *ca.* 1.56–1.64 (*m*, 2 H); *ca.* 1.69–1.81 (*m*, 2 H); *ca.* 1.91–1.97 (*m*, 1 H); *ca.* 2.01–2.16 (*m*, 2 H); *ca.* 2.24–2.33 (*m*, 1 H). ^{13}C-NMR: 226.83, 60.67, 58.62 (3 *s*); 60.03, 44.24 (2 *d*); 37.31, 37.27, 35.34, 35.13, 33.65, 29.86 (6 *t*); 19.55, 16.50 (2 *q*). MS: 192 (M^+, $C_{13}H_{20}O$), 164, 135 (100), 121, 107, 94, 79, 55.

*(−)-(3a*R*,5a*S*,6*R*,8a*S*)-4,5,5a,6,7,8-Hexahydro-3a,6-dimethylcyclopenta[c]pentalen-3(3a*H*)-one* ((−)-**13**). *a*) The trimethylsilyl 2-en-3-ol ether of (−)-**12** was formed nearly quantitatively by following the procedure for the preparation of **4**.

b) To a stirred soln. of the trimethylsilyl 2-en-3-ol ether of (−)-**12** (185 mg, 0.7 mmol; see *a*)) in benzene (15 ml) at r.t. was added portionwise *N,O*-bis(trimethylsilyl)-2,2,2-trifluoroacetamide (0.5 ml, 1.9 mmol) and DDQ (0.277 g, 1.22 mmol). After being stirred at r.t. for 48 h, the orange soln. was evaporated and chromatographed on silica gel (25 g, hexane/Et_2O 15:1). Pure (−)-**13** was isolated as an oil (95.4 mg, 68.4%; > 98% purity). $[\alpha]_D = -90.4°$ (*c* = 0.71). IR: 1695, 1587. ^{1}H-NMR: 0.97 (*d*, *J* = 6.3, 3 H); 1.00 (*s*, 3 H); *ca.* 1.22–1.51 (*m*, 4 H); *ca.* 1.54–1.89 (*m*, 5 H); *ca.* 1.96–2.02 (*m*, 1 H); 5.94 (*d*, *J* = 5.5, 1 H); 7.42 (*d*, *J* = 5.5, 1 H). ^{13}C-NMR: 216.19, 66.34, 57.59 (3*s*); 171.07, 128.70, 58.43, 39.28 (4 *d*); 35.88, 35.39, 30.38, 26.03 (4 *t*); 20.48, 19.24 (2 *q*). MS: 190 (M^+, $C_{13}H_{18}O$), 175 (100), 162, 147, 135, 119, 105, 91, 79, 65, 55. Anal. calc. for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 82.15, H 9.57.

(−)-Silphiperfol-6-en-5-one ((−)-**14**). To a suspension of CuI (0.164 g, 0.86 mmol) in Et_2O (12 ml) at 0° were added 1.08 ml of a MeLi soln. (1.72 mmol; 1.6M in Et_2O). When this mixture turned clear after 15 min, (−)-**13** (83 mg, 0.43 mmol) in THF (3 ml) was added dropwise. A yellow suspension formed which was stirred at 0° for 1 h before HMPA (2 ml) and MeI (0.3 ml) were added simultaneously. After 10 min the mixture was poured into H_2O/Et_2O, 10% aq. NH_3 soln. was added dropwise until all solid particles were dissolved, the org. phase was

separated, washed consecutively with H_2O and brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue (silica gel, 100-fold; hexane/Et_2O 50:1) gave the 6,7-dihydro derivative of (−)-**14** (75.3 mg, 78.4%; 94% purity; skeletal numbering adopted from [4]) as a C(6) epimeric mixture (full spectroscopic analysis). This material was converted to (−)-**14** by repeating the procedure for (−)-**12**→(−)-**13**, except that the step with DDQ was done at 45°. Purification of the resultant oil was achieved on silica gel (100-fold, hexane/Et_2O 30:1) affording white, crystalline (−)-**14** (40.1 mg, 52% overall yield; > 97% purity). M.p. 52°. IR, MS, ^{1}H- and ^{13}C-NMR, and $[\alpha]_D = -39.5°$ ($c = 0.34$) agree with the data reported for (−)-**14** [4].

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