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A NEW AND FACILE PERHYDROAZULENE FORMATION : THE TOTAL SYNTHESIS OF THE CAROTANE (+)-DAUCENE

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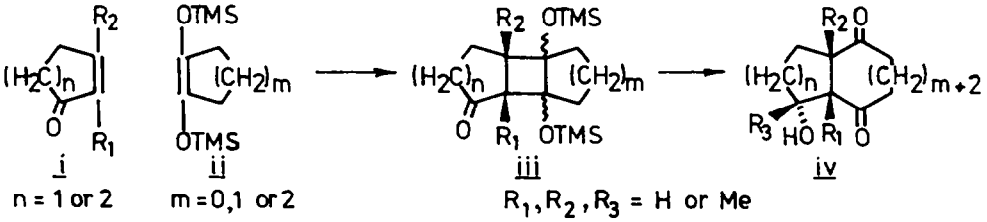
Summary : Thermolysis of the 2,5-bis(trimethylsiloxy)tricyclo[4.4.0.$0^{2,5}$]decan-7-ones 3 leads to perhydroazulenes by a transannular reaction involving an oxygen to oxygen migration of a silyl group in the intermediate cyclodecadienones. This 3-step transformation of a 2-cyclohexenone into a perhydroazulene is illustrated by the synthesis of the carotane (+)-daucene (5).

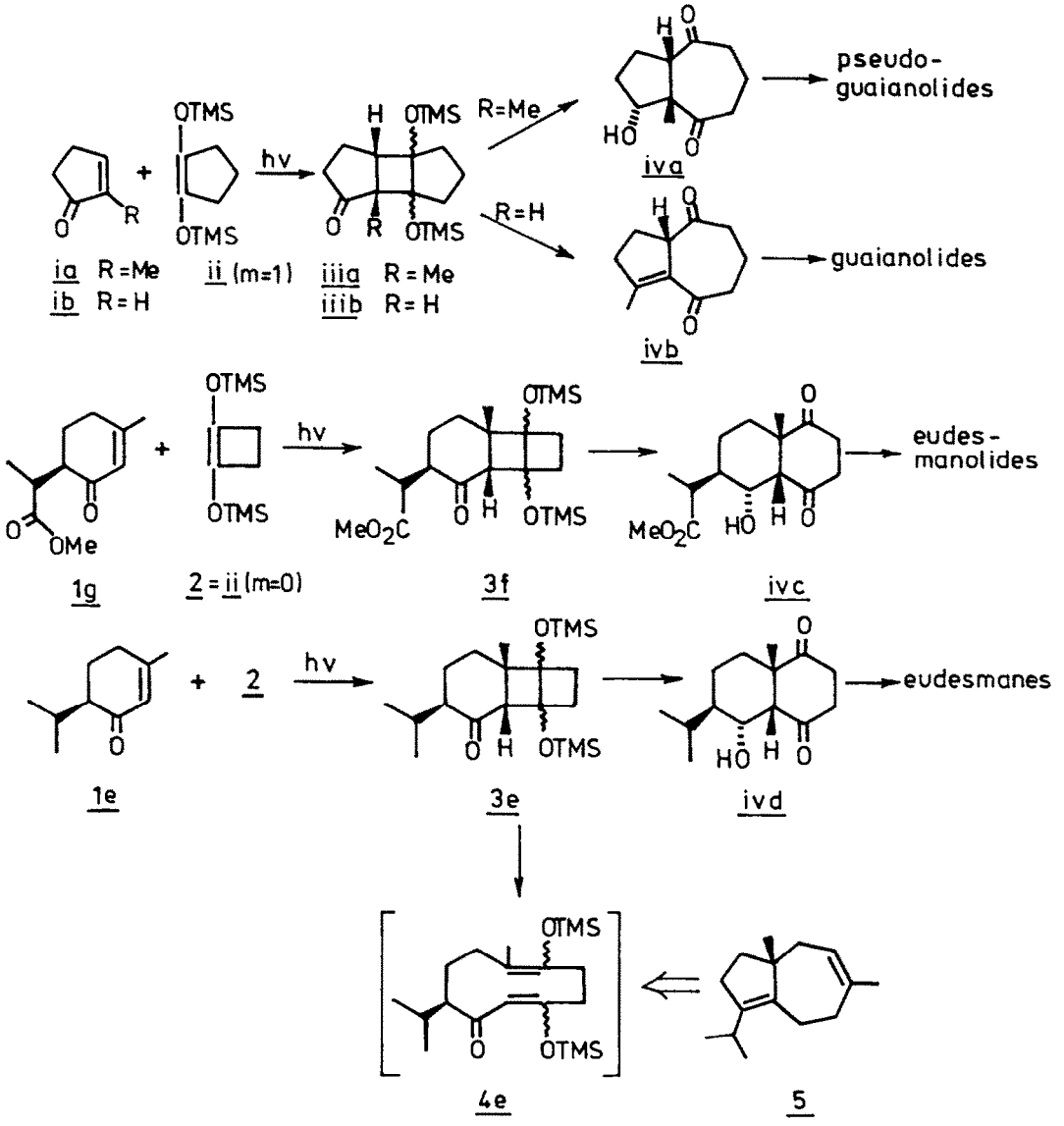
During the last ten years our interest in sesquiterpene chemistry was mainly devoted to the total synthesis of target molecules, possessing a γ-lactone nucleus and displaying cytotoxic activity. To a large extent, our efforts were directed towards the perhydroazulene and perhydronaphthalene series and relied on a single, general concept[2] (scheme 1). Central in the strategy stands the construction of bicyclic key-intermediates via a novel annulation method based on an initial (2C + 2C) photocycloaddition reaction of 2-cycloalkenones i with 1,2-bis(trimethylsiloxy)cycloalkenes ii. Subsequent transformation of the keto function in adduct iii and oxidative α-diol cleavage then allow for the facile construction of bicarbocyclic compounds iv (n = 1 or 2 and m = 0, 1 or 2), functionalized at three positions adjacent to the ring fusion. Selection of the substitution pattern (R_1, R_2, R_3 and additional alkyl substituents in ring i) enhances the general and versatile nature of the annulation procedure. This was demonstrated by the total synthesis of a number of pseudoguaianolides[3], guaianolides[4], eudesmanolides[5] and eudesmanes[6] via the respective key-intermediates iva, ivb, ivc and ivd (scheme 2).



SCHEME 1

In order to expand the potential of the photoadducts iii (scheme 1) as synthetic intermediates, we decided to investigate the thermal cycloreversion of the cyclobutane nucleus,

as an alternative for the oxidative α-diol cleavage. This could provide an entry into germacranes and/or elemanes; furthermore as transannular reactions of functionalized 10-membered ring systems are well-known[7], investigation in this direction looked worthwile. After some exploratory experiments we decided to concentrate on the more promising thermolysis of the tricyclo[4.4.0.$0^{2,5}$]decane photoadducts 3 (scheme 2 and table). This process led to a new efficient formation of the perhydroazulene skeleton via a remarkable transannular oxygen to oxygen migration of a trimethylsilyl group in the intermediate cyclodecadienone, such as 4e[8]. This new method is illustrated by the total synthesis of (+)daucene (5)[9,10], starting from (-)piperitone (1e) via the photoadduct 3e.

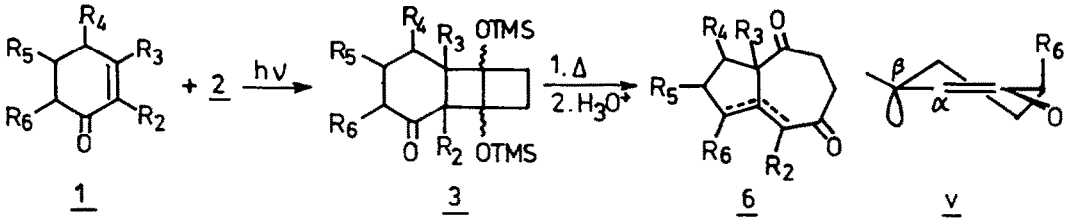


SCHEME 2

In order to delineate the scope of the overall process we have studied the initial photocycloaddition between 1,2-bis(trimethylsiloxy)cyclobutene (2) and a number of substituted 2-cyclohexenones (1) (Table). Photochemical (2C + 2C) reactions involving 2-cyclohexenones are apparently very sensitive to the substitution pattern. This has been attributed among others to the close proximity of the (n,π*) and (π,π*)triplet states thereby allowing for diverse lowest triplet energy behavior[11]. For example, in contrast to 2-methyl-2-cyclopentenone (ia), which gives high yields[2a], 2-methyl-2-cyclohexenone (1c) is a notoriously unreactive substrate in

photocycloadditions[12]. Our purpose was to quickly select those reactions that were amenable to further synthetic elaboration; the quantum yields were not determined. No attempts were made to evaluate the ratio of cis-syn-cis and cis-anti-cis isomers[13], since the stereochemical differentiation is lost during the subsequent thermolysis.

Table : Formation of 3 and 6; yields for the photochemical and thermal reactions.



1 3 6 v

Entry	R_2	R_3	R_4	R_5	R_6	hν : 3 (%)	Δ : 6[d] (%); t; T
a	H	H	H	H	H	46[a]	64; 10 h; 220°C
b	H	Me	H	H	H	79	66 (6b + 6b'); 7 h; 220°C
c	Me	H	H	H	H	no reaction[b]	e
d	Me	Me	H	H	H	40[a]	e
e	H	Me	H	H	i.Pr	85[b]	83; 6 h; 215°C
f	H	Me	H	H	CH_2CO_2Me	68	44; 6.5 h; 210°C
g	H	Me	H	H	$CH(Me)CO_2Me$	60[b]	e
h	H	Me	CO_2Et	H	H	no reaction	e
i	Et	Me	CO_2Et	H	H	25	63 (6i + 6i'); 8 h; 215°C
j	Me	Me	CO_2Me	H	H	18	e
k	H	Me	CH_2OH	H	H	32	e
l	H	Me	CH_2OTMS	H	H	c	e
m	Me	Me	H	CO_2Me	H	c	e
n	Me	CN	H	H	H	96	73 (6n + 6n'); 9 h; 215°C
o	H	CN	H	H	Me	96	e
p	H	CO_2Et	H	H	H	61	e
q	H	Cl	H	H	H	c	e

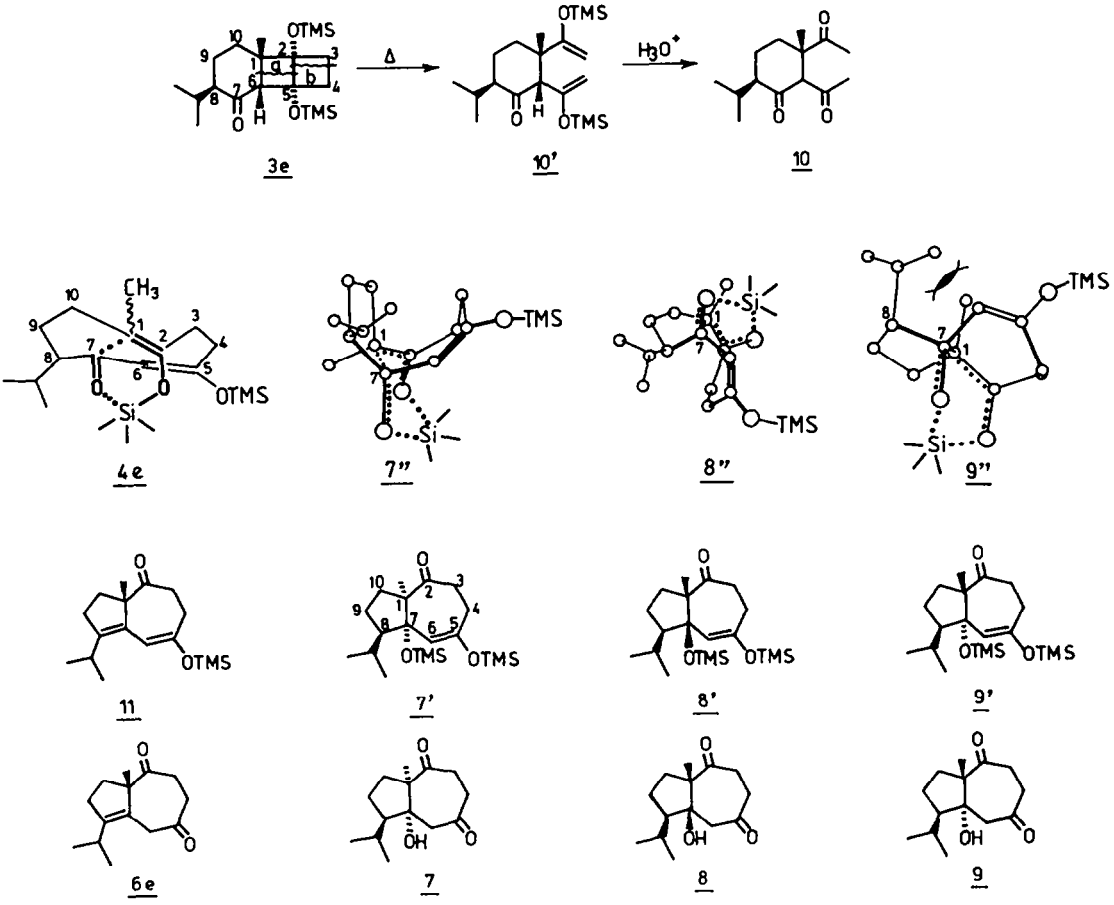
[a] See ref. 6a. [b] See ref. 2b and 5. [c] Unidentified reaction mixture after prolonged irradiation. [d] For structural formulae, see scheme 4. [e] Not studied.

Inspection of the table underlines the known difference in behavior of substrates alkylated at the α-(R_2) or β-position (R_3) of the enone. With regard to the unreactivity of 2-methyl-2-cyclohexenone (entry c) we decided to study the influence of an electron-withdrawing group at the β-position; this could sufficiently alter the energy levels of the excited states (vide supra). As can be seen (entry n) a 3-cyano substituent has a dramatic influence (compare entries c, d, n and o) as almost quantitative yields are observed.

Interestingly, substrates carrying a R_4 and/or R_5 substituent are either photostable, give low yields or are converted to complex reaction mixtures (entries h → m); this stands in sharp contrast to the 6-substituted substrates (entries e, f, g, o), which give good yields and lead to synthetically interesting adducts 3. Furthermore the reaction has a high stereoselectivity and gives predominantly the adduct 3 with R_3 and R_6 in a cis relation. The high selectivity obtained with (-)piperitone (1e) has also been observed by others[7i,j,l]. Comparison of the cis-trans ratios found for 1f (7:3) and 1g (9:1), respectively, shows the enhanced selectivity for a more space demanding group[5]. This is in accord with Wiesner's rule, which proposes that the excited state of an enone is best visualized with the α-atom trigonal and the β-atom pyramidal in its most stable configuration[14]. Thus, due to the $A^{1,2}$-strain, the excited state represented by v

becomes of increasing importance when R_6 is bulkier. When the reaction occurs at the β-atom, cycloaddition anti to R_6 is expected to be the preferred pathway.

The study of the thermolysis of the photoadducts 3 was carried out with 3e as the most representative member (scheme 3; for reasons of clarity, the perhydroazulene numbering is used for the photoadducts 3). Of importance for the elucidation of the mechanism (vide infra) is the fact that 3e is an optically active compound. Starting from the naturally occurring (-)-piperitone (1e; 55 % ee)[15] the same enantiomeric excess is expected for 3e, as a result of the stereoselective photocycloaddition. Heating a benzene solution of 3e in a sealed tube at 215°C for 6 h and subsequent acid treatment yielded the perhydroazulenic diketone 6e in 83 % yield.



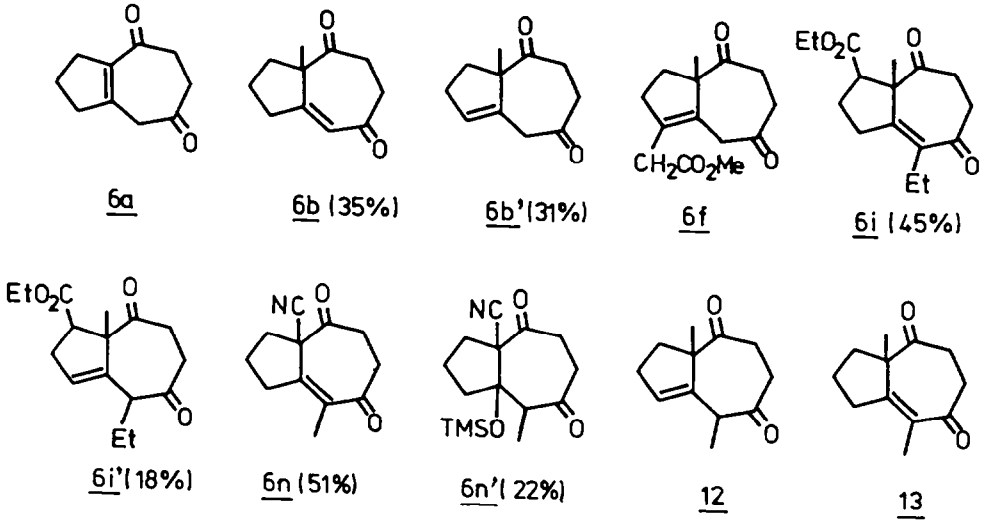
SCHEME 3

The essential step in the formation of 6e is a thermal oxygen to oxygen migration of a trimethylsilyl group (ene reaction type) in the intermediate cyclodecadienone 4e (scheme 3). The transannular reaction of the 10-membered ring occurs during the thermolysis and not during the hydrolysis. Indeed, cleavage of the silyl ethers in the intermediate would afford a cyclodeca-1,3,6-trione, which would be expected to undergo an internal aldol condensation yielding a bicyclo[5.3.0]dec-1-ene-2,10-dione. The proposed thermal reaction is confirmed by spectral data of the crude thermolysis mixture. The ^1H NMR shows an intense singlet (angular methyl) at δ = 1.1 and a broad singlet for a vinylic proton at δ = 5.6. The IR spectrum reveals the presence of an isolated keto function (1710 cm^{-1}) and of a double bond (1660 cm^{-1}). These data are consistent with the gross planar structures of intermediates such as 7', 8', 9' and 11. The substrate for further work (synthesis of (+)-daucene 5; vide infra) 6e has the (1S)-configuration and is formed in ca. 50 % ee. This indicates that the major pathway must involve intermediates 8' and/or 9', respectively, arising from the cis-cis (transition state 8") and the

trans(1,2)-cis(5,6) (transition state 9") cyclodecadienone 4e. Analysis (GC-MS) of several thermolytic experiments shows that increasing the temperature and the time enhances sharply the formation of 11 and suppresses the formation of 10'. The presence of intermediate 11 shows that the thermal elimination of trimethylsilanol from 7', 8' and/or 9' is also a pathway for 6e.

An experiment involving heating for 2.5 h at 215°C and subsequent mild hydrolysis of the silyl ethers allowed the isolation of only two intermediate alcohols 7 (9 %) and 8 (21 %) next to 6e (54 %) and two isomers of triketone 10 (10 %). Only 7 gave correct crystals for structure determination by single-crystal X-ray diffraction[16]. The tentative structure 8 for the other alcohol follows from the observation that both ^{1}H NMR spectra are very analogous; the almost identical chemical shifts for the angular methyl protons (δ = 1.28 and 1.29) suggest a cis ring-fusion in both cases[3a,17]. The optical purity of 8 could be determined by means of the chiral shift reagent tris 3-(heptafluoropropylhydroxymethylene)-d-camphorato europium(III); measurements of the methyl protons of the isopropyl group indicated an ee of ca. 56 %, again showing the stereoselectivity of the photochemical and thermal processes.

The metathetical cleavage (a) of 3e must lead, when assuming a concerted reaction, to the cis-trans cyclodecadienones, while the divinylcyclohexanone 10' arises from cleavage (b) or through Cope rearrangement after cleavage (a). The cis-cis isomer (its intermediacy being proven by the presence of 7) is produced from the cis-trans isomers by two successive Cope rearrangements (via 10'). It is evident that because of geometrical constraints the isomeric 1-cis,5-trans-cyclodecadienone cannot undergo the transannular reaction. Calculations[18] show that in transition state 7" the nascent 7-membered ring has to take a high-energetic 6-/E conformation for allowing the silyl group migration. This corroborates with the observed absolute configuration of 6e; indeed the enantiomer (via 7') is the minor product. For 8" and 9" the growing 7-membered ring takes a 2-/B and 2-/C conformation, respectively. However, the non-observation of 9 could be due to its more elusive nature because of more facile trimethylsilanol elimination in 9' to 11. In conclusion, perhydroazulene 6e is formed from 1e in three steps with an overall yield of 71 % and with high chirality transfer of C-6 in 1e to the angular position in 6e.

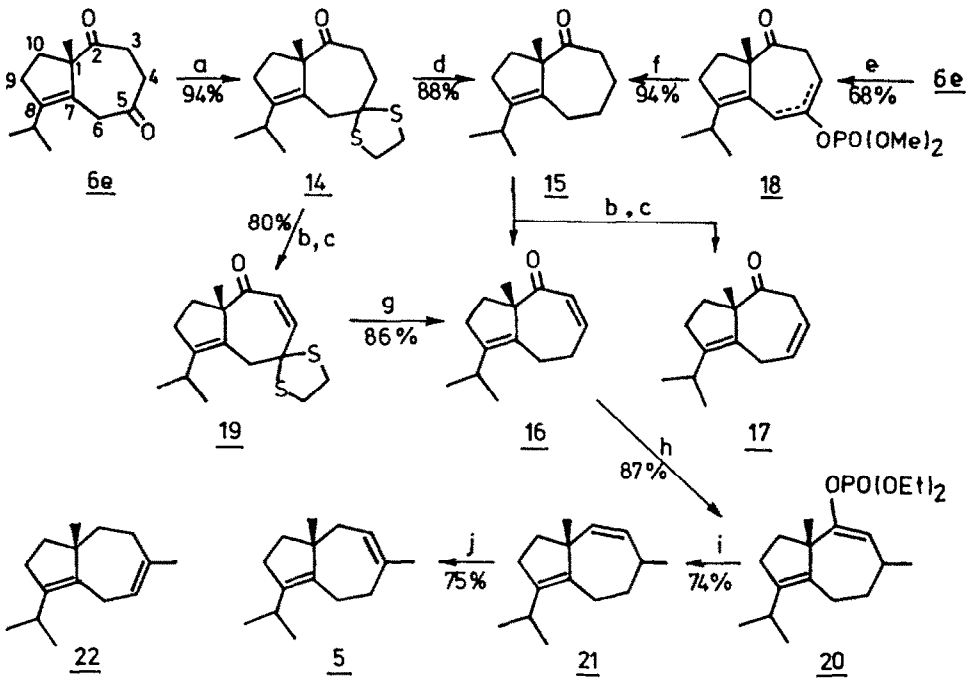


SCHEME 4

The results for the thermolysis of other photoadducts are given in the table and scheme 4. The indicated reaction times are for the reaction leading only to bicyclo[5.3.0]decane skeletons. As observed for 3e, shorter reaction times invariably led to the formation of substituted cyclohexanones as byproducts (vide supra). Only one major perhydroazulene derivative was identified for the simplest photocycloadduct (entry a) and for the compounds 3 carrying substituents at C-1 and C-8 (entries e and f). While in 6a the conjugated double bond is

situated between the bridgehead carbon atoms, both in 6e and 6f the double bond is contained within the 5-membered ring. In the absence of a C-8 substituent (entries b and i) two positional isomers were found with a preference for the conjugated isomer (6b > 6b'; 6i > 6i'). It is worth mentioning that methylation of 6b and 6b' exclusively led to the monoalkylated pseudoguaiane precursor 12 (80 %); treatment with DBU provoked shifting of the double bond to 13 (85 %). In addition to the expected 6n, a potential pseudoguaiane precursor, the trimethylsilyl ether 6n' (diastereomeric mixture) was isolated. The stability of 6n' under acidic conditions is intriguing and could be due to the cis position of the trimethylsiloxy group with respect to the cyano group.

In order to determine the absolute configuration of 6e we decided to transform it into (+)-daucene (5) (scheme 5). (+)-Daucene, with known absolute configuration, is a member of the sesquiterpene group of the carotanes[9,10]. The transformation of the key-intermediate 6e into (+)-daucene (5) involves the removal of the two carbonyl functions while introducing a methyl group and a double bond. Considering the positions of the carbonyl groups it is clear that one or both can serve as handles for introducing the new functions. Therefore the two keto groups have to be differentiated and a sequential removal had to be planned. The approach shown in scheme 5 became especially attractive when it was observed that mono-dithioacetal formation of the 5-keto group was highly regioselective; this is probably due to steric reasons. In contrast, reaction with glycol led to a mixture of the monoprotected and diprotected derivatives.



(a) $(CH_2SH)_2$, $BF_3.Et_2O$, CH_2Cl_2; (b) $PhSO_2Me$, KH, THF, Δ; (c) toluene, Na_2CO_3, Δ; (d) Raney-Ni(W-4), MeOH, Δ, 24 h; (e) LDA, $ClPO(OMe)_2$, THF, -78°C → rt; (f) Pt-C, H_2, EtOH; (g) deactivated Raney-Ni(W-4) (prior reflux in Me_2CO), EtOH, Δ, 6h; (h) Me_2CuLi, Et_2O, -15°C, then $ClPO(OEt)_2$, Et_3N; (i) Li, $EtNH_2$, t.BuOH, THF; (j) $RhCl_3.3H_2O$, EtOH, 100°C, 4 h.

SCHEME 5

Desulfuration of 14 afforded the monoketone 15 in high yield. An alternative procedure for the formation of 15 became available when it was observed that selective formation of the enol phosphonates 18[19] of the 5-carbonyl group was possible. It was our intention to introduce the methyl substituent via conjugate addition on the enone 16. However treatment of 15 with methyl benzene sulfinate followed by thermal elimination led to 16, highly contaminated with the non-conjugated isomer 17. We therefore decided to change the sequence and to introduce the double bond prior to the removal of the dithioacetal. Application of Monteiro's method[20] afforded 19 in

excellent yield. The planned conjugate addition (Me_2CuLi, Et_2O at -30°C) on 19 failed to produce the methylated products. Instead reduction of the conjugated double bond and partial hydrogenolysis of the thioacetal was observed[21]. This result forced us to consider again the intermediacy of enone 16. We hereby hoped that desulfuration of 19 would give access to pure 16. However, treatment of 19 with an excess Raney-nickel (W-4) led with concomittant double bond reduction to ketone 15 in 94 % yield. Fortunately this side reaction could be circumvented by prior deactivation of the Raney-Ni (W-4)[22]; under these conditions desulfuration of 19 led to the conjugated enone 16 as the sole product. Conjugate addition and trapping of the enolate anion as the enol phosphonate afforded 20, which upon reductive cleavage[23] gave 21 as a single epimer with undefined configuration at C-4. Finally, Grieco's procedure for double bond migration[24] gave (+)-daucene (5) next to iso-daucene (22) in a ratio 3:1. Both isomers could be separated on silver nitrate impregnated silica gel. Synthetic 5 has the same sign of optical rotation as naturally occurring (+)-daucene thereby proving the absolute configuration of the key-intermediate 6e resulting from (-)piperitone 1e in the 3-step photochemical, metathetical and ene reaction sequence. The measured $[\alpha]_D^{23}$-value of +20.8° corresponds with ca.50 % ee for 5. This again shows the high chirality transfer of the 6-position in (-)-piperitone 1e (55 % ee) to the angular position in 6e, indicating that the pathway through 7" (scheme 3) is the least favored one.

The total synthesis of (+)-daucene (5) starting from 1e involves 10 steps and has an overall yield of ca 22 %. Other applications of this efficient perhydroazulene formation from 2-cyclohexenones are presently under study.

EXPERIMENTAL SECTION

The melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 337 spectrophotometer, mass spectra on a AEI MS-50 spectrometer and GC-MS spectra on a Finnigan 3200 instrument. The ^1H NMR spectra were recorded at 90 MHz (Varian EM-390) or at 360 MHz (Bruker WH-360) in $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Rf values are quoted for Merck silica gel 60 GF_{254} TLC plates of thickness 0.25 mm. Optical rotations were measured at the sodium D line on a Perkin-Elmer 141 polarimeter using a 1 dm-cell.

Reaction products were isolated by the addition of water and extraction with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed from the filtered solution on a rotary evaporator. Column chromatographic purifications were performed on silica gel. HPLC purifications (silica gel) were carried out with the Waters Ass. Prep. LC/System 500 apparatus.

2-Cyclohexenone (1a), Hagemann's ester (1h) and 2-ethyl-Hagemann's ester (1i) were purchased from Janssen Chimica, Beerse, Belgium. (-)Piperitone (1e) was a gift from Roure Bertrand Dupont S.A., Grasse, France. 3-Methyl-2-cyclohexenone (1b)[25], 4-carbomethoxy-2,3-dimethyl-2-cyclohexenone (1j)[26], 5-carbomethoxy-2,3-dimethyl-2-cyclohexenone (1m)[27], 3-carbethoxy-2-cyclohexenone (1p)[28], 3-chloro-2-cyclohexenone (1q)[29] and 1,2-bis(trimethylsiloxy)cyclobutene (2)[30] were prepared according to known procedures. Kinetic enolate formation (LDA) and trapping with methyl 2-bromoacetate (in HMPA) afforded 6-carbomethoxymethyl-3-methyl-2-cyclohexenone (1f). 3-Methyl-4-hydroxymethyl-2-cyclohexenone (1k) was obtained from 1h via sequential reduction ($LiAlH_4$, Et_2O, -20°C, 100 %) to the diol and oxidation (MnO_2, benzene, 83 %) of the allylic alcohol[31]. Conversion of 1k to the corresponding trimethylsilyl ether 11 was achieved by selective protection of the primary alcohol (t.BuMe$_2$SiCl, Et_3N, CH_2Cl_2, DMAP, 49 %) followed by allylic oxidation (pyridinium dichromate, CH_2Cl_2, 55 %)[32].

3-Cyano-6-methyl-2-cyclohexenone (1o) and 3-cyano-2-methyl-2-cyclohexenone (1n)

To a solution of 6-methyl-2-cyclohexenone[33] (4.54 mmol, 0.5 g) in CCl_4 (6 ml) was added Br_2 (1 eq, 4.54 mmol, 7.62 mg, 233 l) in CCl_4 (5 ml) at 10°C. Addition of pyridine (1.5 ml) after 2 min led to precipitation of 2-bromo-6-methyl-2-cyclohexenone (635 mg, 74 %).
IR (neat) : 3030-2800, 1676, 1600 cm^{-1}; MS (EI) : m/z (%) : 190 ($M^{+\cdot}$, 76), 188 ($M^{+\cdot}$, 78); 149 (20), 148 (100), 146 (100), 120 (50), 118 (50), 109 (44); ^1H NMR : δ (90 MHz) : 1.22 (d, J 6.75 Hz, 3H); 1.91-1.76 (m, 1H), 2.05-2.18 (m, 1H), 2.43-2.52 (m, 2H), 2.52-2.64 (m, 1H), 7.35 (dt, J 4.00 and 1.00 Hz, 1H).
A solution of 2-bromo-6-methyl-2-cyclohexenone (2.12 mmol, 400 mg), KCN (1.3 eq, 2.76 mmol, 180 mg) and NH_4Cl (1 eq, 2.12 mmol, 113 mg) in DMF (15 ml) and MeOH (10 ml) was stirred at rt for 20 h. Treatment with $NaHCO_3$ satd, extraction (ether) washing (HCl 1 N and then $NaHCO_3$ satd) and drying ($MgSO_4$) furnished after HPLC-purification (EtOAc/hexane 1:9) 3-cyano-6-methyl-2-cyclohexenone (204 mg, 71 %).
Rf (EtOAc/hexane 2:8) : 0.24; IR (neat) : 3000-2820, 2223, 1687, 1610 cm^{-1}; ^1H NMR : δ(360 MHz) : 1.18 (d, J 6.75 Hz, 3H), 1.83 (dddd, J 13.75, 12.25, 9.75 and 2.75 Hz, 1H), 2.17 (dddd, J 13.75,

9.50, 4.50 and 1.00 Hz, 1H), 2.47 (ddq, J 12.25, 6.75 and 4.50 Hz, 1H), 2.70-2.54 (m, 2H), 6.50 (dd, J 2.50 and 1.25 Hz, 1H).
The same procedure was applied for the preparation of 3-cyano-2-methyl-2-cyclohexenone (1n) starting from 2-methyl-2-cyclohexenone (1b) (57 %).

General procedure for the photocycloaddition between 1 and 2

Substrate 1 (25 mmol) and 2 (125 mmol) in pentane (150 ml) were irradiated (Rayonet photochemical reactor; The Southern New England Ultraviolet Company, Hamden, Connecticut 06514, USA) at 350 nm ($n - \pi^*$ excitation of 1) under N_2. The reaction was monitored by TLC. After complete conversion the solvent was removed and the residue was purified (Kugelrohr distillation or preparative column chromatography).

(1S,6R,8R)1-Methyl-2,5-bis(trimethylsiloxy)-8-isopropyltricyclo|4.4.0.$0^{2,5}$|decan-7-one (3e)

A solution of R(-)-piperitone (1) ($|\alpha|_D^{23}$ = -28.5° (c 0.616, MeOH), 19.5 g, 128 mmol) and 2 (85.5g, 0.37 mmol) in pentane (300 ml) for 8 days. Distillation gave 3e (44 g, 85 %; bp 130-140°C/0.05 mm Hg).
Rf (EtOAc/isooctane 1:9) : 0.44; IR (neat) : 1710, 1385, 1365, 1250, 1050 cm^{-1}; MS (CI, isobutane) : m/z (%) : 383 ($M^{+\cdot}$, 11), 312 (1), 293 (2), 231 (16), 225 (46), 153 (100); MS (EI) : m/z (%) : 382 ($M^{+\cdot}$, 1), 367 (2), 270 (18), 269 (23), 73 (100); ^{1}H NMR : δ (360 MHz) : 0.11 (s, 9H), 0.16 (s, 9H), 0.78 (d, J 6.75 Hz, 3H), 0.92 (d, J 6.75 Hz, 3H), 1.03 (s, 3H), 2.45 (s, 1H).

General procedure for the thermolysis of 3

A solution of photoadduct 3 (10 mmol), in benzene (7 ml) was transferred into a dry tube (borosilicate glass). The tube was sealed off in vacuo under N_2 and heated in an electrical oven (usually several hours at a temperature 200°C). After cooling the solution was diluted with ether (1 ml), HCl (10 N, 4 ml) was added dropwise at 0°C and the mixture was stirred for 3 h at rt. Washing ($NaHCO_3$ satd, 2 x), extraction and concentration gave a residue, which was further purified by preparative column chromatography).
For yields and specific conditions of the thermolyses : see table.

(1S)-1-Methyl-8-isopropylbicyclo|5.3.0|dec-7-ene-2,5-dione (6e)

Rf (EtOAc/isooctane 1:9) : 0.30; IR (neat) : 3000-2840, 1707, 1480-1420 cm^{-1}; MS (EI) : m/z (%) : 220 ($M^{+\cdot}$, 15), 192 (10), 177 (20), 150 (13), 149 (100), 121 (40); ^{1}H NMR : δ(360 MHz) : 0.95 (d, J 6.80 Hz, 3H), 0.99 (d, J 6.80 Hz, 3H), 1.26 (s, 3H), 1.65 (m, 1H), 2.08-2.57 (m, 4H), 2.48-2.87 (m, 4H), 3.06 (dt, J 14.20 and 1.65 Hz, 1H), 3.39 (d, J 14.20 Hz, 1H); $|\alpha|_D^{23}$ = -105.7° (c 0.083, $CHCl_3$).

Bicyclo|5.3.0|dec-1(7)-ene-2,5-dione (6a)

Rf (EtOAc/isooctane 3:7) : 0.17; UV : λ_{max} : 255 nm; IR (neat) : 3000-2820, 1712, 1655 cm^{-1}; MS (EI) : m/z (%) : 164 ($M^{+\cdot}$, 92), 135 (30), 121 (14), 109 (30), 108 (100), 107 (33); ^{1}H NMR : δ (90 MHz) : 1.70-2.10 (m, 2H), 2.50-3.05 (m, 8H), 3.60 (s, 2H).

1-Methylbicyclo|5.3.0|dec-6-ene-2,5-dione (6b)

Rf (EtOAc/isooctane 4:6) : 0.27; UV : λ_{max} : 240 nm; IR (neat) : 3040-2810, 1700, 1660, 1470 cm^{-1}; MS (EI) : m/z (%) : 179 (12), 178 ($M^{+\cdot}$, 100), 163 (14), 153 (15), 135 (56), 122 (44), 121 (37), 111 (38), 107 (33) ; ^{1}H NMR : δ(90 MHz) :1.48 (s, 3H), 1.67-2.60 (m, 6H), 2.60-3.13 (m, 4H), 6.16 (s, 1H).

1-Methylbicyclo|5.3.0|dec-7-ene-2,5-dione (6b')

Rf (EtOAc/isooctane 4:6) : 0.37; IR (neat) : 3040, 3000-2840, 1705, 1640, 1460-1400 cm^{-1}; MS (EI) : m/z (%) : 178 ($M^{+\cdot}$, 12) 138 (17), 95 (100); ^{1}H NMR : δ (360 MHz) : 1.32 (s, 3H), 1.71-1.82 (m, 1H), 1.92-2.01 (m, 1H), 2.32-3.00 (m, 6H), 3.24 (dm, J 14.80 Hz, 1H), 3.39 (d, J 14.80 Hz, 1H), 5.75 (m, 1H).

1-Methyl-8-carbomethoxymethylbicyclo|5.3.0|dec-7-ene-2,5-dione (6f)

Rf (EtOAc/isooctane 5:5) : 0.31; IR (neat) : 3000-2840, 1735, 1700, 1670, 1435 cm^{-1}; MS (EI) : m/z (%) : 250 ($M^{+\cdot}$, 40); 222 (20), 207 (13), 163 (60), 151 (52), 149 (62), 148 (84), 107 (100, 106 (40), 105 (39); ^{1}H NMR : δ(360 MHz) : 1.31 (s, 3H), 1.31 (m, 1H), 1.78 (m, 1H), 2.35-2.68 (m, 6H), 2.87 (m, 1H), 3.15 (d, J 15.00 Hz, 1H), 3.16 (s, 2H), 3.35 (d, J 15.00 Hz, 1H), 3.67 (s, 3H).

10-Carbethoxy-6-ethyl-1-methylbicyclo[5.3.0]dec-6-ene-2,5-dione (6i)

Rf (EtOAc/isooctane 2:8) : 0.09; IR (neat) : 3010-2820, 1730, 1710, 1190 cm^{-1}; MS (EI) : m/z (%) : 278 ($M^{+\cdot}$, 10), 205 (33), 108 (100), 107 (96), 79 (100); ^1H NMR : δ(360 MHz) : 0.83 (t, J 7.00 Hz, 3H), 1.27 (t, J 7.00 Hz, 3H), 1.41 (s, 3H), 1.45-2.03 (m, 5H), 2.46-2.70 (m, 3H), 3.17 (dd, J 10.75 and 2.75 Hz, 1H), 3.33-3.45 (m, 1H), 3.71 (dd, J 10.75 and 2.76 Hz, 1H), 4.17 (m, 2H).

10-Carbethoxy-6-ethyl-1-methylbicyclo[5.3.0]dec-7-ene-2,5-dione (6i')

Rf (EtOAc/isooctane 2:8) : 0.19; UV : λ_{max} : 260 nm; IR (neat) : 3020-2820, 1730, 1710, 1660 cm^{-1}; MS (EI) : m/z (%) : 278 ($M^{+\cdot}$, 16), 205 (33), 108 (100), 107 (97), 79 (100); ^1H NMR : δ (360 MHz) : 0.97 (t, J 7.25 Hz, 3H), 1.28 (t, J 7.00 Hz, 3H), 1.20-1.36 (m, 2H), 1.43 (s, 3H), 2.00-3.00 (m, 9H), 4.14 (dq, J 11.00 and 7.00 Hz, 1H), 4.16 (dq, J 11.00 and 7.00 Hz, 1H).

1-Cyano-6-methylbicyclo[5.3.0]dec-6-ene-2,5-dione (6n)

Rf (EtOAc/hexane 2:8) : 0.22; IR (neat) : 3010-2820, 2222, 1725, 1665, 1622 cm^{-1}; MS (EI) : m/z (%) : 203 ($M^{+\cdot}$, 7), 176 (65), 175 (33), 148 (54), 147 (40), 135 (51), 133 (26), 107 (100), 104 (20); ^1H NMR : δ (360 MHz) : 1.90 (t, J 1.50 Hz, 3H), 1.93-2.93 (m, 8H), 3.07 (ddd, J 17.25, 5.50 and 3.00 Hz, 1H), 3.81 (ddd, J 15.00, 12.75 and 5.50 Hz, 1H).

1-Cyano-6-methyl-7-trimethylsiloxybicyclo[5.3.0]deca-2,5-dione (6n')

Rf (EtOAc/hexane 1:9) : 0.24; IR (neat) : 3020-2820, 2125, 1700 cm^{-1}; MS (EI) : m/z (%) : 293 ($M^{+\cdot}$, 16), 166 (100); ^1H NMR : δ (360 MHz) : 0.08 (s, 9H), 0.12 (s, 9H), 1.23 (d, J 6.75 Hz, 3H), 1.62 (d, J 7.55 Hz, 3H), 3.04-3.34, 2.38-2.84 and 1.85-2.27 (3 x m, 21H), 3.54 (q, J 6.75 Hz, 1H).

(1R,7S,8R)-7-Hydroxy-1-methyl-8-isopropylbicyclo[5.3.0]deca-2,5-dione (7), its C-1,C-7 diastereomer (8) and (3S,6R)-2,3-diacetyl-3-methyl-6-isopropylcyclohexanone (10)

Photocycloadduct 3e (26.1 mmol, 10 g) dissolved in benzene (20 ml) was heated in a sealed borosilicate glass tube for 3.5 h at 200°C. After cooling the solution was diluted with diethylether (30 ml) and acidified with HCl (5N, 10 ml). Stirring for 4 h at rt, washing with satd Na_2CO_3, work-up and column chromatography (EtOAc/isooctane 1:9, then 2:8) allowed isolation of 4 compounds : 6e (3.1 g, 54 %), 7 (0.56 g, 9 %), 8 (1.3 g, 21 %) and 10 (0.625 g, 10 %). Separation between 7 and 8 could only be achieved by HPLC (EtOAc/hexane 35:65). Compound 10 was a mixture of 2 epimers.

7 : Rf (EtOAc/hexane 35:65) : 0.21; mp : 114°C; IR (0.005 M in CCl_4) : 3600-3300, 3000-2880, 1700 cm^{-1}; MS (EI) : m/z (%) : 153 (31), 140 (39), 139 (41), 138 (23), 125 (24), 123 (26), 97 (100); ^1H NMR : δ (360 MHz) : 0.93 (d, J 6.50 Hz, 3H), 1.09 (d, J 6.50 Hz, 3H), 1.28 (s, 3H), 1.53-1.64 (m, 2H) 1.64-1.78 (m, 1H), 1.88-2.00 (m, 1H), 2.28-2.43 (m, 2H), 2.39 (d, J 13.5 Hz, 1H), 2.47-2.59 (m, 1H), 2.75 (dd, J 13.5 and 1.75 Hz, 1H); $[\alpha]_D^{23}$ = +6.70° (c 0.069, $CHCl_3$).

8 : Rf (EtOAc/hexane 35:65) : 0.18; mp : 121.5°C; IR (0.005 M in CCl_4) : 3640, 3360, 3000-2880, 1705 cm^{-1}; MS (EI) : m/z (%) : 238 ($M^{+\cdot}$, 19), 220 (12), 140 (40), 139 (61), 138 (25), 125 (22), 123 (20), 99 (45), 97 (100); ^1H NMR : δ (360 MHz) : 0.95 (d, J 6.85 Hz, 3H), 1.01 (d, J 6.85 Hz, 3H), 1.29 (s, 3H), 1.30-1.39 (m, 1H), 1.41-1.56 (m, 2H), 1.71-1.85 (m, 2H), 1.92 (s, 1H), 2.13-2.25 (m, 1H), 2.41-2.52 (m, 1H), 2.53-2.60 (m, 1H), 2.64 (d, J 13.60 Hz, 1H), 2.69-2.78 (m, 1H), 2.85 (dd, J 13.60 and 0.76 Hz, 1H), 3.09-3.22 (m, 1H); $[\alpha]_D^{23}$ = +6.74° (c 0.074, $CHCl_3$).

10 : Rf (EtOAc/isooctane 2:8) : 0.22; IR (neat) : 3400, 3000-2860, 1700, 1600 cm^{-1}; MS (EI) : m/z (%) : 195 (28), 153 (100); ^1H NMR : δ (90 MHz) : 0.81 (d, J 6.90 Hz, 3H), 0.88 (d, J 6.90 Hz, 3H), 0.89 (d, J 6.75 Hz, 3H), 0.91 (d, J 6.75 Hz, 3H), 1.33 (s, 3H), 1.40 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H), 2.20 (s, 3H), 3.83 (s, 1H), 4.15 (s, 1H).

(1S)-5,5-Ethylenedithio-1-methyl-8-isopropylbicyclo[5.3.0]dec-7-en-2-one (14)

A solution of 6e (100 mg, 0.45 mmol), ethane dithiol (55.7 mg, 0.59 mmol) and $BF_3.Et_2O$ (15 1) in CH_2Cl_2 (2 ml) was stirred for 3 h at rt. Work-up and HPLC-purification (EtOAc/hexane, 5:95) gave 14 (127 mg, 94 %, mp 84°C).

Rf (EtOAc/hexane 35:65) : 0.21; IR (KBr) : 2970-2780, 1690 cm^{-1}; MS (EI) : m/z (%) : 296 ($M^{+\cdot}$, 1), 281 (1), 265 (6), 137 (22), 121 (22), 99 (100); ^1H NMR : δ(360 MHz) : 0.93 (d, J 6.75 Hz, 3H), 1.12 (s, 3H), 1.14 (d, J 6.75 Hz, 3H), 1.60 (ddd, J 12.10, 5.60 and 3.75 Hz, 1H), 1.85 (dt, J 12.10 and 9.00 Hz, 1H), 2.04-2.41 (m, 4H), 2.46 (d, J 13.50 Hz, 1H), 2.97 (h, J 6.75 Hz, 1H), 3.04-3.47 (m, 7H); $[\alpha]_D^{23}$ = +5.4° (c 0.120, $CHCl_3$).

(1S)-1-Methyl-5-(dimethoxy)phosphonoxy-8-isopropylbicyclo|5.3.0|deca-5,7-dien-2-one and the isomeric 4,7-diene (18)

To a solution of 6e (19 mg, 0.086 mmol) in dry THF (1 ml), at -78°C, was added LDA (0.086 mmol, 1.1 M solution) in THF. After stirring for 15 min, dimethyl chlorophosphate (13.7 mg, 0.095 mmol) was added and stirring was continued for 45 min, with slow warming up to rt. Work-up and HPLC (EtOAc-hexane 6:4) gave the two isomeric 18.
The 5,7-diene (7.5 mg, 26 %); Rf (EtOAc/hexane 5:5) : 0.50; IR (neat) : 3040-2800, 1700, 1660, 1610, 1450, 1360, 1280, 1045 cm^{-1}; MS (EI) : m/z (%) : 328 ($M^{+\cdot}$, 5), 300 (3), 285 (18), 165 (37), 159 (76), 145 (30), 131 (97), 127 (70), 117 (35), 105 (36), 96 (100); ^1H NMR : δ(360 MHz) : 1.00 (d, J 6.75 Hz, 3H), 1.03 (d, J 6.75 Hz, 3H), 1.25 (s, 3H), 1.74 (dt, J 13.00 and 5.40 Hz, 1H), 2.01 (dt, J 13.00 and 8.60 Hz, 1H), 2.29-2.43 (m, 3H), 2.61-2.70 (m, 2H), 2.74 (h, J 6.75 Hz, 1H), 3.07 (ddd, J 12.50, 10.50 and 6.00 Hz, 1H), 3.83 (dd, J 11.00 and 0.50 Hz, 6H), 6.23 (s, 1H).
The 4,7-diene (12 mg, 42 %); Rf (EtOAc/hexane 3:5) : 0.53; IR (neat) : 3000-2820, 1710, 1290, 1050 cm^{-1}; MS (EI) : m/z (%) : 328 ($M^{+\cdot}$, 10), 300 (5), 285 (20), 159 (55), 151 (37), 149 (37), 131 (72), 127 (50), 117 (33), 105 (30), 41 (100); ^1H NMR : δ(360 MHz) : 1.00 (s, J 6.75 Hz, 3H), 1.03 (d, J 6.75 Hz, 3H), 1.29 (s, 3H), 1.68 (ddd, J 12.75, 9.00 and 6.75 Hz, 1H), 2.08 (ddd, J 12.75, 8.5 and 5.75 Hz, 1H), 2.09-2.42 (m, 2H), 2.57 (dd, J 13.25 and 10.00 Hz, 1H), 2.78 (h, J 6.75 Hz, 1H), 2.93 (dm, J 16.50 Hz, 1H), 3.53 (dm, J 16.50 Hz, 2H), 3.81 (dd, J 11.10 and 1.25 Hz, 6H), 5.41 (dm, J 10.00 Hz, 1H).

(1S)-1-Methyl-8-isopropylbicyclo|5.3.0|dec-7-en-2-one (15)

a. From 14 : A mixture of 14 (100 mg, 0.34 mmol) and Raney-Ni (W-4, 300 mg) in MeOH (10 ml) was refluxed for 24 h. Filtration, solvent evaporation and HPLC (EtOAc/hexane 2.5:97.5) gave 15 (61 mg, 88 %).
b. From 18 : A mixture of 18 (25 mg, 0.075 mmol) and Pt-C (5 %, 5 mg) in EtOH (2.5 ml) was stirred under H_2 (atm. press.) for 5 h. Filtration on Celite and HPLC-purification gave 15 (14.8 mg, 94 %).
Rf (EtOAc/hexane 1:9) : 0.29; IR (neat) 3000-2840, 1730, 1450 cm^{-1}; MS (EI) : m/z (%) : 206 ($M^{+\cdot}$, 8), 163 (7), 147 (10), 145 (10), 136 (27), 135 (100), 121 (31), 107 (49); ^1H NMR : δ(360 MHz) : 0.98 (d, J 6.75 Hz, 3H), 1.08 (d, J 6.75 Hz, 3H), 1.13 (s, 3H), 1.24-1.48 (m, 2H), 1.53-1.65 (m, 2H), 1.80-1.94 (m, 3H), 2.16-2.25 (m, 1H), 2.29-2.40 (m, 2H), 2.55 (dm, J 14.00 Hz, 1H), 2.69-2.81 (m, 2H); $|\alpha|_D^{23}$ = +30.0° (c 0.025, $CHCl_3$).

(1S)-5,5-Ethylenedithio-1-methyl-8-isopropylbicyclo|5.3.0|deca-3,7-dien-2-one (19)

A solution of 14 (710 mg, 2.38 mmol) in dry THF (10 ml) was added to KH (573 mg, 4.76 mmol) and methyl benzenesulfinate (744 mg, 4.76 mmol) in dry THF (20 ml). The mixture was refluxed for 3 h; after cooling ether was added and the solution was washed with satd NH_4Cl. Work-up and solvent evaporation gave crude sulfoxide which was dissolved in toluene (30 ml). Na_2CO_3 (1 g, 9.5 mmol) was added and the suspension was refluxed for 5 h. Filtration on Celite and HPLC (EtOAc/hexane 5:95) gave 18 (568 mg, 80 %).
Rf (EtOAc/hexane 5:95) : 0.16; UV : λ_{max} : 223 nm; IR (neat) : 3040-2940, 1680, 1660, 1630, 1465, 1330 cm^{-1}; MS (EI) : m/z (%) : 294 ($M^{+\cdot}$, 9), 279 (3), 266 (31), 251 (9), 238 (25), 223 (34), 191 (22), 158 (28), 131 (100), 129 (25), 128 (25), 121 (34), 118 (94), 115 (34), 107 (25), 105 (34); ^1H NMR : δ (360 MHz) : 0.93 (d, J 6.50 Hz, 3H), 1.11 (d, J 6.50 Hz, 3H), 1.20 (s, 3H), 1.68 (dt, J 12.50 and 5.50 Hz, 1H), 1.97 (dt, J 12.50 and 8.50 Hz, 1H), 2.26 (m, 2H), 2.85 (d, J 13.90 Hz, 1H), 3.02 (h, J 6.50 Hz, 1H), 3.24 (dd, J 13.90 and 1.75 Hz, 1H), 3.32-3.54 (m, 4H), 5.62 (d, J 12.50 Hz, 1H), 6.26 (dd, J 12.50 Hz and 1.75 Hz, 1H); $|\alpha|_D^{23}$ = +8.8° (c 0.445, $CHCl_3$).

(1S)-1-Methyl-8-isopropylbicyclo|5.3.0|deca-3,7-dien-2-one (16)

A suspension of Raney-Ni (W-4, 100 mg) in acetone (10 ml) was refluxed for 1 h. After cooling the acetone was decanted and the residue was washed with dry EtOH (3 x 5 ml). The deactivated Raney-Ni and 19 (100 mg, 0.34 mmol) in EtOH (3 ml) were refluxed for 6 h. Work-up and HPLC (EtOAc/hexane 2.5:97.5) gave 16 (60 mg, 86 %).
Rf (EtOAc/hexane 5:95) : 0.23; UV : λ_{max} : 223 nm; IR (neat) : 2980-2800, 1655, 1450 cm^{-1}; MS (EI) : m/z (%) : 204 ($M^{+\cdot}$, 2), 189 (2), 133 (19), 119 (25), 115 (28), 107 (20), 105 (38), 41 (100); ^1H NMR : δ (360 MHz) : 0.98 (d, J 6.75 Hz, 3H), 1.00 (d, J 6.75 Hz, 3H), 1.25 (s, 3H), 1.65 (ddd, J 12.00, 7.25 and 3.75 Hz, 1H), 2.08 (dt, J 12.00 and 7.75 Hz, 1H), 2.14-2.34 (m, 4H), 2.47-2.63 (m, 2H), 2.69 (h, J 6.75 Hz, 1H), 5.90 (ddd, J 12.50, 2.25 Hz and 1.50 Hz, 1H), 6.26 (dddd, J 12.50, 4.75, 3.25 and 1.00 Hz, 1H); $|\alpha|_D^{23}$ = +23.2° (c 0.280, $CHCl_3$).

(1S)-1,4-Dimethyl-2-(diethoxy)phosphonoxy-8-isopropylbicyclo|5.3.0|deca-2,7-diene (20)

To a suspension of Cu_2I_2 (70 mg, 0.37 mmol) in dry Et_2O (3 ml) at -15°C was added MeLi (5.05 ml, 1.45 M solution, 0.73 mmol). After stirring for 10 min a solution of 16 (25 mg, 0.12 mmol) in Et_2O (2 ml) was added dropwise, followed by Et_3N (61.7 mg, 0.61 mmol) and diethyl chlorophosphate (63.2 mg, 0.36 mmol). The mixture was stirred for 1 h and then poured in Et_2O (20 ml), satd

NH_4Cl (5 ml) and NH_4OH (5 ml, 6 % solution). Work-up and HPLC (EtOAc/hexane 3:7) gave 20 (38 mg, 87 %).
Rf (EtOAc/hexane 3.7) : 0.23; IR (neat) : 3020-2820, 1660, 1450, 1275, 1100-950 cm^{-1}; ^1H NMR : δ(360 MHz) : 0.85 (d, J 6.75 Hz, 3H), 0.89 (d, J 7.00 Hz, 3H), 0.92 (d, J 7.00 Hz, 3H), 1.28 (tm, J 7.00 Hz, 6H), 1.14 (s, 3H), 1.54-1.63 (m, 2H), 1.80-1.91 (m, 2H), 1.99-2.16 (m, 3H), 2.30-2.40 (m, 1H), 2.48-2.57 (m, 1H), 2.60 (h, J 7.00 Hz, 1H), 4.09 (dm, J 7.00 Hz, 4H), 5.31 (dd, J 2.00 and 4.00 Hz, 1H); $|\alpha|_D^{23}$ = -12.3° (c 0.011, $CHCl_3$).

(1R)-1,4-Dimethyl-8-isopropylbicyclo|5.3.0|deca-2,7-diene (21)

To a solution of 20 (16.5 mg, 0.046 mmol) in THF (0.5 ml) and t.BuOH (21.7 µl, 0.23 mmol) was added, at 0°C, Li (3.5 mg, 0.5 mmol) in $EtNH_2$ (3 ml) and THF (0.5 ml). After stirring for 1 h the mixture was poured in ice-water. Work-up and HPLC (EtOAc/hexane 2.5:97.5) gave 21 (7 mg, 74 %).
Rf (EtOAc/hexane 2.5:97.5) : 0.60; IR (neat) : 3020-2800, 1450 cm^{-1}; ^1H NMR : δ (360 MHz) : 0.95 (d, J 6.75 Hz, 3H), 0.97 (d, J 6.75 Hz, 3H), 1.00 (d, J 7.25 Hz, 3H), 1.12 (m, 3H), 1.59-1.71 (m, 1H), 1.71-1.89 (m, 3H), 1.98-2.08 (m, 1H), 2.09-2.25 (m, 2H), 2.34-2.47 (m, 1H), 2.60-2.74 (m, 2H), 5.20 (ddd, J 11.90, 3.45 and 0.95 Hz, 1H), 5.54 (dd, J 11.90 and 2.50 Hz, 1H); $|\alpha|_D^{23}$ = +9.0° (c 0.007, $CHCl_3$).

(+)-Daucene (5)

A solution of 21 (2 mg, 0.01 mmol) and $RhCl_3.3H_2O$ (0.26 mg, 0.001 mmol) in EtOH (0.5 ml) was heated in a sealed tube at 100°C for 4 h. After addition of satd $NaHCO_3$ (0.25 ml) the products were isolated upon extraction with diethylether and usual work-up. Column chromatography on silica gel, impregnated with $AgNO_3$ (EtOAc/hexane 2.5:97.5), gave (+)-daucene (5, 1.5 mg, 75 %).
Rf (EtOAc/hexane 2.5:97.5) : 0.62; ^1H NMR: δ(360 MHz) : 0.99 (d, J 6.60 Hz, 3H), 1.01 (d, J 6.60 Hz, 3H), 1.23 (s, 3H), 1.57 (s, 3H), 1.63 (ddd, J 13.30, 8.25 and 5.25 Hz, 1H), 2.06 (m, 1H), 2.28 (m, 1H), 2.69-3.03 (m, 6H), 3.33 (d, J 17.50 Hz, 1H), 3.57 (dp, J 12.50 and 2.00 Hz, 1H), 5.53 (m, 1H); $|\alpha|_D^{23}$ = +20.8° (c 0.0015, $CHCl_3$).

1,6-Dimethylbicyclo|5.3.0|dec-6-ene-2,5-dione (13)

To a solution of 6b and 6b' (15 mg, 0.084 mmol) in t.BuOH (0.5 ml) and THF (0.5 ml) was added at rt t.BuOK (2 eq, 18.9 mg, 0.168 mmol) and MeI (5 eq, 59.6 mg, 26.1 l, 0.42 mmol). Work-up after 2 h and HPLC-purification (EtOAc/hexane 1:9) gave 12 (13 mg, 80 %).
Compound 12 (13 mg, 0.068 mmol) was dissolved in CH_2Cl_2 (2 ml), 1,8-diazabicyclo|5.4.0|undec-7-ene (DBU, 10 µl) was added and the solution was stirred for 15 h. Work-up and HPLC (EtOAc/hexane 1:9) afforded 13 (11 mg, 85 %).
Rf (EtOAc/hexane 2:8) : 0.17; ^1H NMR : δ(90 MHz) : 1.38 (s, 3H), 1.86 (t, J 1.30 Hz, 3H), 1.66-2.19 and 2.46-3.06 (2 x m, 1H).

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