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Protoilludane sesquiterpenes: synthesis of (±)-cerapicol, formal synthesis of (±)-sterpurene, and synthesis and absolute configuration of (+)-cerapicol☆

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ABSTRACT

New approaches to the protoilludane sesquiterpenes (±)-cerapicol and (±)-sterpurene via rearrangement routes are described. The absolute configuration of (+)-cerapicol has been determined and found in accord with a biosynthesis of the natural product via cyclization of humulene to the so-called protoilludyl cation and a subsequent 1,2-alkyl shift.

1. Introduction

Protoilludane sesquiterpenes arise from cyclization of humulene **1** to the so-called protoilludyl cation **5** and subsequent transformations, in particular 1,2-alkyl shifts.[2] A central part of the resulting 'protoilludane tree' comprises the cations **3**–**6** and the sesquiterpenes (+)-sterpurene **9**,[3] (+)-cerapicol **10**,[4] (−)-Δ^6-protoilludene **11**,[5] and (+)-ceratopicanol **12**[6] derived there from (Scheme 1). Of these, **10**[4a] and **12**[6a] were detected last and taken as evidence that two long-sought links (**4**, **6**) within the biosyntheses of (+)-sterpurene **9** (**1**-**5**-**4**-**3**-**9**)[3b–d] and (+)-hirsutene **2**[7] (**1**-**5**-**6**-**7**-**8**-**2**) had been identified.[8] However, an examination of the absolute configurations known so far reveals that (+)-sterpurene [(+)-(2a*S*,3a*S*,7a*S*)-**9**][3e,f] and (+)-ceratopicanol [(+)-(1*R*,3a*R*,3b-*S*,6a*S*,7a*S*)-**12**][6b] may well be formed via **5**, but not (+)-hirsutene [(+)-(3a*R*,3b*R*,6a*R*,7a*S*)-**2**].[7b–e] Indeed, convincing evidence exists that the biosynthesis of (+)-**2** begins with a cyclization of humulene **1** to *ent*-**6** and proceeds via *ent*-7 and *ent*-**8** to (+)-**2**.[9] Therefore, in the strict sense, hirsutanes are not protoilludanes.

Of the sesquiterpenes with unknown absolute configuration, (+)-cerapicol **10** is the only compound with the skeleton of **4**. In contrast, sesquiterpenes with the skeleton of **5** are abound and not restricted to (−)-Δ^6-protoilludene (−)-**11**. Significantly, in all derivatives examined,[10] the absolute configuration proved in accord with a biosynthesis via **5**. Assuming the same to be true for (−)-**11**, we thought it would be most valuable to determine the absolute configuration of (+)-**10**, and to check its compatibility with a biosynthesis of (+)-**10** via **4**.

Toward this end, and under the condition of a resolution of ketone **13**, we could have used our previous synthesis of (±)-**10** [**13**-**14**-**10**(**15**,**16**)][4c] directly (Scheme 2). However, this synthesis is hampered by the fact that the trifluoroacetic acid induced rearrangement of the vinylcyclobutane **14** proceeds with preferential protonation at C-3 leading to the undesired norbornanes **15** and **16** as main products. Therefore, two alternatives for a hopefully more selective conversion of **14** to **10** were examined.

The first alternative was to transform the vinylcyclobutane **14** to the epoxide **17** prior to a rearrangement. With **17**, a ring enlargement of the 3,3-dimethyl-cyclobutyl ring seemed not to be inhibited, and even in case that the 1,3-bridge would form first, we expected the olefin **18** as stabilomer of seven isomers[4c] and as a potential precursor of (±)-**10** (**14**-**17**-**18**-**10**) as the final product (Scheme 2). The second alternative was to transform the epoxide **17** to the α-hydroxyketone **19** as a promising candidate for a rearrangement to the enone **20**[11] as a potential precursor of the ketone **21**. Given the fact that **21** had previously been transformed to (±)-sterpurene **9**,[3i,k,l] and the latter to (±)-cerapicol **10**,[4b] a synthesis of **21** (**17**-**19**-**20**-**21**)

☆ Cascade Rearrangements: Part 25. For part 24, see Ref. 1.

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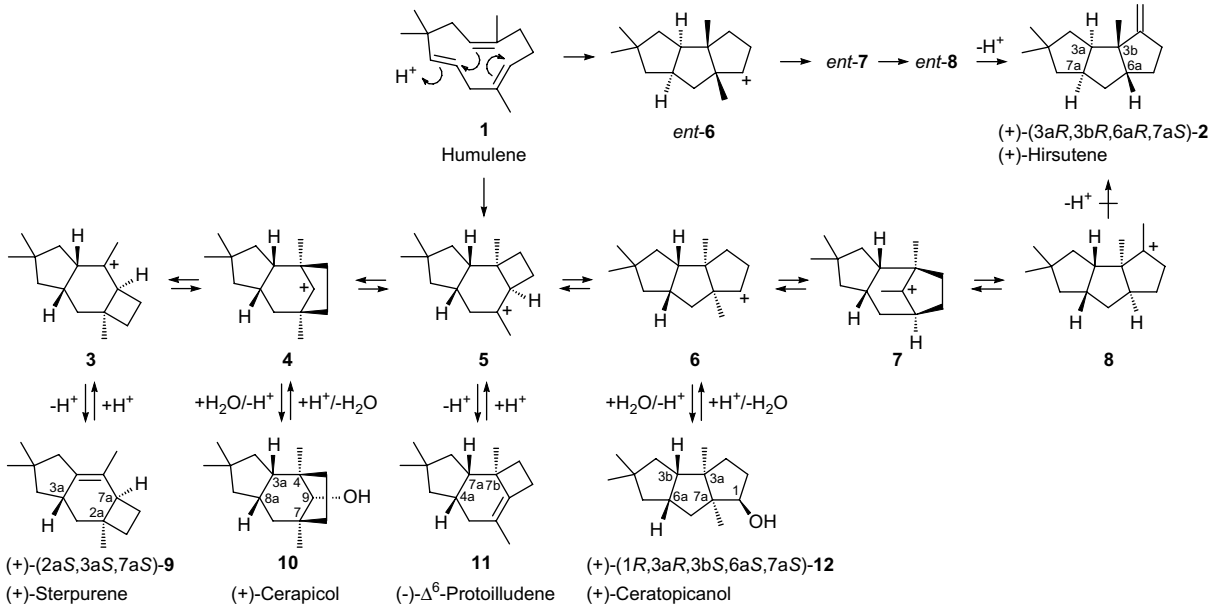
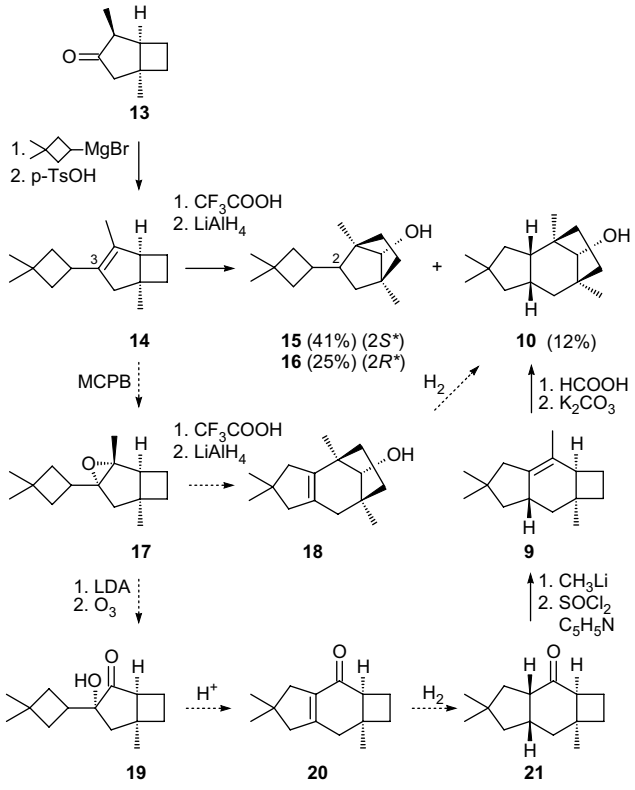


Scheme 1.



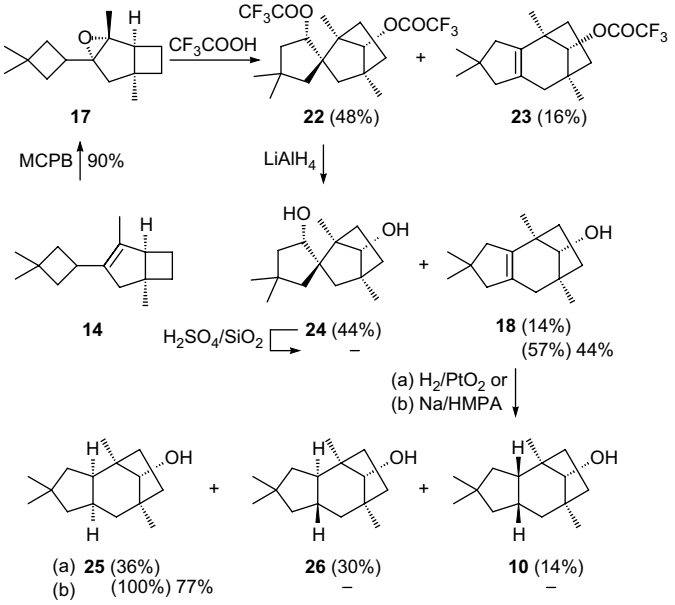
Scheme 2.

would not only have constituted a formal synthesis of (±)-**9**, but would also have opened another possibility for a determination of the absolute configuration of (+)-**10** (**21**-**9**-**10**). The necessary resolution at the stage of ketone **13** seemed feasible.

2. Results

2.1. Synthesis of (±)-cerapicol [(±)-10]

To explore the possibility of a synthesis of (±)-cerapicol [(±)-**10**] via the olefin **18** we subjected the vinylcyclobutane **14** first to a buffered epoxidation and obtained a single epoxide thought to be formed by an attack of the reagent from the less hindered side of **14** and formulated as **17** (Scheme 3). On treatment with trifluoroacetic acid in pentane, **17** rearranged to yield a mixture of trifluoroacetates containing 48% of **22** and 16% of **23**. Pure samples were obtained by a combination of thick layer and gas chromatography, and their structures were established by NMR. However, the configuration of **22** is tentative and implies that **17** rearranges with inversion of configuration at the migration origins and termini. In any case, the preferred formation of **22** indicates that the cyclopentyl cation formed by enlargement of the 3,3-dimethyl-cyclobutyl ring is effectively trapped.



Scheme 3.

As could have been expected, the reduction of the mixture of trifluoroacetates with lithium aluminum hydride delivered a mixture of alcohols containing 44% of **24** and 14% of **18**. Once again,

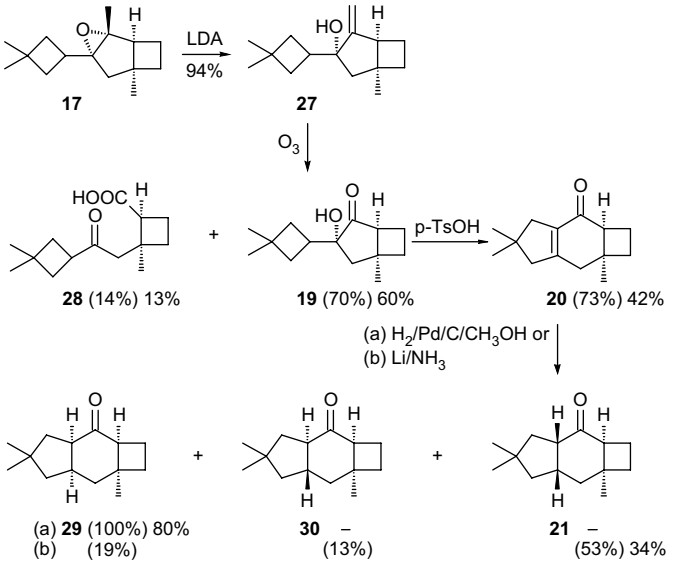
pure samples were obtained by a combination of thick layer and gas chromatography, and once again their structures resulted from an analysis of their NMR data. At this stage, a rearrangement of **24** to **18** seemed feasible. Toward this end, we treated a solution of the mixture of alcohols in hexane with 5% (w/w) sulfuric acid on silica gel. After 42 h at 50 °C **24** had disappeared and the content of **18** had risen to 57%. Upon chromatography on silica gel in pentane/ether 7:3, 44% of **18**, as referred to **17**, were obtained pure.

To our disappointment, the hydrogenation of **18** did not proceed as desired. A hydrogenation over Pd/C in methanol failed, a hydrogenation over platinum dioxide in acetic acid yielded the undesired diastereoisomers **25** (36%) and **26** (30%) instead of **10** (14%) as main products, and a hydrogenation with sodium in hexamethylphosphoramide (HMPA) containing *tert*-butyl alcohol[12] delivered **25** exclusively. Of the products formed, **25** was identified by an analysis of its ^{1}H NMR, ^{13}C NMR, HETCOR, COSY, and NOESY spectra, **26** by means of an X-ray analysis, and **10** via its known ^{1}H and ^{13}C NMR data.[4c] Clearly, the low yield in the hydrogenation step made the synthesis of **10** via **18** much less attractive than the direct synthesis from **14**. Therefore, the second alternative of a synthesis via sterpurene **9** was examined.

2.2. Formal synthesis of (±)-sterpurene [(±)-9]

For the synthesis of the α-hydroxyketone **19** as a potential precursor of the enone **20**, and hence of the ketone **21**, we treated the epoxide **17** with lithium diisopropyl amide (LDA) and subjected the resulting allylic alcohol **27**[13] to an ozonolysis. The reaction progress was monitored by GC and stopped after **27** had been consumed. At this time, the reaction mixture contained 70% of the desired α-hydroxyketone **19** and 14% of the δ-keto-acid **28** as product of an 'anomalous' ozonolysis.[14] Chromatography on silica gel in pentane/ether 7:3 yielded 60% of pure **19** (mp 59 °C) and 13% of pure **28** (mp 50–52 °C). The structure and configuration of **19** followed from an X-ray analysis, which indicated that the structure and configuration of **17** and **27** were also correct. The rearrangement of **19** was induced by treatment with 4 equiv of a 0.15 molar solution of anhydrous *p*-toluenesulfonic acid in benzene. After 7 h at 80 °C, the concentration of **20** had reached its maximum (73%), and work up and chromatography on silica gel in pentane/ether 7:3 then yielded **20** in 42% isolated yield (Scheme 4).

In contrast to **18**, the hydrogenation of **20** over Pd/C proceeded smoothly and yielded a single product. However, to our disappointment, an analysis of its ^{1}H NMR, ^{13}C NMR, HETCOR, COSY, and NOESY spectra revealed that this product was the undesired *cis-syn-cis* configured ketone **29**. Fortunately, switching to lithium in liquid ammonia as the reducing system[15] reversed the stereochemistry. The desired *cis-anti-cis* configured ketone **21**[3m] (53%) was now the main product, followed by **29** (19%) and **30**[3i,n] (13%) (Scheme 4). Interestingly, **21** proved to be unstable in $CDCl_3$ and slowly epimerized to yield, at equilibrium, a 7:3 mixture with **30**. This equilibrium could almost instantaneously be established by use of Nafion NR 50 in benzene. Of the products formed, **21** was isolated by chromatography on silica gel in pentane/ether 9:1 (R_f=0.27; yield 34%). Under these conditions, **29** and **30** (R_f=0.33) were eluted as mixture. However, pure **30** could be obtained after epimerization of **21** by gas chromatography.

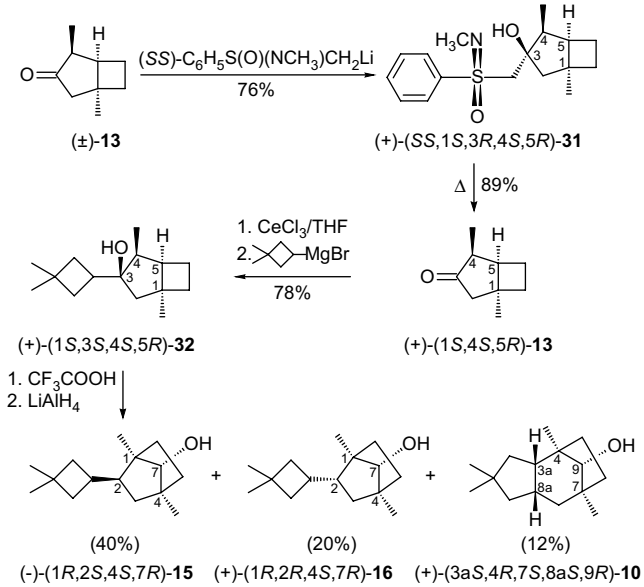


Scheme 4.

From a preparative point of view, the overall yield of **21** from **17** (8%) was too low as to allow an economic synthesis of (±)-cerapicol **10** via (±)-sterpurene **9** (**21**-**9**-**10**) (Scheme 2). Therefore, for the determination of the absolute configuration of (+)-cerapicol (+)-**10**, we turned to our original synthesis of (±)-**10**.[4c]

2.3. Synthesis and absolute configuration of (+)-cerapicol [(±)-10]

The synthesis of enantiopure cerapicol **10** via the vinylcyclobutane **14** required a resolution of the racemic ketone (±)-**13**. According to a general method of Johnson et al.[16a,b] we treated (±)-**13** with lithiated (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine[16c–e] and obtained four diastereoisomeric β-hydroxy-sulfoximines (^{1}H NMR). Upon chromatography on silica gel in pentane/ether 7:3, the first eluted diastereoisomer (mp 150–152 °C) was obtained pure and an X-ray analysis disclosed its identity as (*SS*,1*S*,3*R*,4*S*,5*R*)-**31** (>99% ee, $[\alpha]_D^{20}$ +88.3 (*c* 1.22, $CHCl_3$)). The subsequent fragmentation proceeded smoothly and delivered the enantiomerically pure ketone (1*S*,4*S*,5*R*)-**13** (purity 99% GC, >99% ee, $[\alpha]_D^{20}$ +78.7 (*c* 1.41, acetone)) (Scheme 5).



Scheme 5.

The remaining steps were performed as described for the synthesis of (±)-**10**.[4c] Addition of 3,3-dimethyl-cyclobutylmagnesium bromide to (1*S*,4*S*,5*R*)-**13** yielded the alcohol (1*S*,3*S*,4*S*,5*R*)-**32** (purity 99% GC, >99% ee, $[\alpha]_D^{20}$ +22.9 (*c* 1.39, acetone)), and subsequent treatment with trifluoroacetic acid followed by reduction with lithium aluminum hydride delivered, with the transient formation of **14**, the norbornane (−)-(1*R*,2*S*,4*S*,7*R*)-**15** (purity 99% GC, >99%

ee, $[\alpha]_D^{20}$ −33.8 (*c* 1.35, acetone)), the norbornane (+)-(1*R*,2*R*,4*S*,7*R*)-**16** (purity 99% GC, >99% ee, $[\alpha]_D^{20}$ +75.5 (*c* 1.36, acetone)), and (+)-cerapicol [(+)-(3a*S*,4*R*,7*S*,8a*S*,9*R*)-**10**] (purity 99% GC, >99% ee, $[\alpha]^{20}$ (nm) +25.2 (589), +26.3 (578), +30.0 (546), +49.9 (436), +73.9 (365) (*c* 1.00, $CHCl_3$)). In the case of (+)-**10**, the optical rotations perfectly matched those of the natural product ($[\alpha]^{20}$ (nm) +24.7 (589), +26.0 (578), +29.3 (546), +48.8 (436), +73.9 (365) (*c* 1.00, $CHCl_3$)). This means that the absolute configuration of the natural product is undoubtedly (3a*S*,4*R*,7*S*,8a*S*,9*R*), which is in accord with a biosynthesis of (+)-**10** via **4** (Scheme 1).

In summary, we have developed a new synthesis of racemic cerapicol [(±)-**10**] and a new formal synthesis of racemic sterpurene [(±)-**9**]. Moreover, we have determined the absolute configuration of natural (+)-cerapicol [(+)-**10**] as (3a*S*,4*R*,7*S*,8a*S*,9*R*). This configuration is in accord with a biosynthesis of (+)-**10** via **4**. Of the methods employed, the rearrangement of **19** to **20** should also have potential for a synthesis of other systems with a 1,2,3,5,6,7-hexahydro-inden-4-one substructure.

3. Experimental

3.1. General

IR spectra were obtained with a Perkin–Elmer 298 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR 500, VXR 600 or a Bruker AMX 300 spectrometer. As standards the following chemical shifts were used: δ_H ($CHCl_3$)=7.24, δ_H (C_6D_5H)=7.15, δ_C ($CDCl_3$)=77.00, δ_C (C_6D_6)=128.00. ^{13}C multiplicities were studied by ATP and/or DEPT and/or HMQC measurements. Mass spectra were obtained with a Finnegan MAT 95 spectrometer (EI and HREI) operated at 70 eV. Only fragment ions with a relative intensity of ≥20% are given. Optical rotations were measured on a Perkin–Elmer 241 digital polarimeter in a 1 dm cell. Analytical and preparative GC was carried out on a Carlo Erba 6000 Vega 2 instrument using a thermal conductivity detector and hydrogen as carrier gas. The following columns were used: (A): 3 m×1/4″ all-glass system, 15% FFAP on Chromosorb W AW/DMCS 60/80 mesh; (B): 3 m×1/4″ all-glass system, 15% OV 210 on Chromosorb W AW/DMCS 60/80 mesh. Product ratios were not corrected for relative response. R_f values are quoted for Machery and Nagel Polygram SIL G/UV_{254} plates. Colorless substances were detected by oxidation with 3.5% alcoholic 12-molybdophosphoric acid and subsequent warming. Melting points were observed on a Reichert microhotstage. Boiling and melting points are not corrected. Microanalytical determinations were done at the Microanalytical laboratory of the Institute of Organic and Bioorganic Chemistry, Göttingen.

3.2. *rel*-(1*S*,2*R*,4*R*,6*S*)-4-(3,3-Dimethyl-cyclobutyl)-2,6-dimethyl-3-oxa-tricyclo[4.2.0.0^{2,4}]octane (17)

To a vigorously stirred mixture of **14**[4c] (7.6 g, 37 mmol) in dichloromethane (225 mL) and 0.5 M aqueous sodium bicarbonate (225 mL) was added within 1 h at 0–5 °C a solution of 3-chloroperoxybenzoic acid (19.4 g, 70% w/w, 80 mmol) in dichloromethane (225 mL). According to TLC [pentane/ether 9:1, R_f=0.74 (**14**), 0.58, 0.50 (**17**)], after additional 0.5 h the reaction was complete. The phases were separated, the aqueous layer was extracted with dichloromethane (2×100 mL), the combined organic layers were washed with 1 N NaOH (2×125 mL), brine (125 mL), and dried ($MgSO_4$). The solvent was distilled off (bath temperature 35 °C/15 Torr) and the residue (8.1 g) chromatographed on silica gel (0.05–0.20 mm) in pentane/ether 9:1 (column 90×6 cm) yielding 7.3 g (90%) of **17** as colorless liquid. ^1H NMR (600 MHz, C_6D_6, C_6D_5H int): δ=1.03 (s, 3H), 1.10 (s, 3H), 1.14 (d, *J*=1.5 Hz, 3H), 1.15 (d, *J*=1.2 Hz, 3H), 1.47 (symm m, 1H), 1.58–1.83 (m, 8H), 1.84 (pseudo s, 2H), 1.96 (pseudo t, 1H), 2.27 (pseudo t, 1H), 2.46 (pseudo quint, 1H); ^{13}C NMR (125.7 MHz, C_6D_6, C_6D_6 int): δ=12.64 (q), 18.22 (t), 28.22 (q), 28.87 (q), 29.65 (d), 30.62 (q), 32.12 (s), 32.96 (t), 36.70 (t), 37.58 (t), 42.01 (s), 44.45 (t), 52.01 (d), 72.56 (s), 75.05 (s); MS (EI): *m*/*z*=220 (3, M^+), 205 (100), 191 (30), 164 (30), 149 (85), 135 (57), 121 (60), 95 (23), 94 (40), 93 (22), 55 (23), 43 (26). Anal. Calcd for $C_{15}H_{24}O$: C, 81.75; H, 10.98. Found: C, 82.04; H, 10.69.

3.3. *rel*-(1*R*,2*R*,2′*S*,4*S*,7*R*)-Trifluoroacetic acid 2′-trifluoroacetoxy-1,4,4′,4′-tetramethyl-spiro{bicyclo[2.2.1]heptan-2,1′-cyclopentan}-7-yl ester (22) and trifluoroacetic acid *rel*-(4*R*,7*S*,9*R*)-2,2,4,7-tetramethyl-1,2,3,4,5,6,7,8-octahydro-4,7-methanoazulen-9-yl ester (23)

To a stirred solution of **17** (3.20 g, 14.5 mmol) in pentane (45 mL) was added within 5 min trifluoroacetic acid (15 mL) causing an exothermic effect. The mixture was stirred at room temperature and the reaction progress was monitored by GC [column B, 160 °C; retention times (min): 1.52, 2.53 (**23**), 3.38, 3.78, 4.42, 5.70, 8.58 (**22**), 10.76]. After 3 h, the mixture did not change further and contained 48% **22**, 16% **23**, and a total of 36% of six unidentified compounds. Water (250 mL) was added, the layers were separated, and the aqueous phase was extracted with pentane (2×50 mL). The combined organic layers were washed with water (2×50 mL), dried (K_2CO_3), and concentrated (bath temperature 35 °C/15 Torr) to yield 4.60 g of a slightly yellow liquid containing the trifluoroacetates. 4.40 g were reduced with $LiAlH_4$ (see Section 3.4) and 0.20 g were purified by thick layer chromatography in pentane [SIL G-100 UV_{254}, 20×20×0.1 cm; R_f=0.1–0.2 (**22**), 0.2–0.3 (**23**)] followed by preparative GC on column B [160 °C; retention time (min): 8.55 (**22**)] and column A [160 °C; retention time (min): 2.87 (**23**)], respectively. Colorless liquids. Compound **22**: ^1H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=0.975 (s, 6H), 0.984 (s, 3H), 1.08 (s, 3H), 1.36–1.50 (m, 5H), 1.57–1.64 (m, 2H), 1.81 (d, *J*=14 Hz, 1H), 2.07 (dd, *J*=12, 7.5 Hz, 1H), 2.21 (dd, *J*=13, 1 Hz, 1H), 4.65 (d, *J*=1 Hz, 1H), 5.08 (dd, *J*=8, 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, $CDCl_3$ int): δ=14.92 (q), 18.15 (q), 29.63 (t), 30.98 (t), 31.08 (q), 31.24 (q), 34.32 (s), 45.24 (t), 45.88 (s), 46.57 (t), 50.75 (s), 52.48 (t), 53.51 (s), 81.18 (d), 91.29 (d), 114.51 (q, $^1J_{CF}$=286 Hz), 114.60 (q, $^1J_{CF}$=286 Hz), 156.68 (q, $^2J_{CF}$=42 Hz), 157.32 (q, $^2J_{CF}$=42 Hz); MS (EI): *m*/*z*=430 (10, M^+), 316 (38), 289 (40), 208 (26), 207 (59), 206 (100), 107 (23), 95 (69), 94 (22), 93 (24). Anal. Calcd for $C_{19}H_{24}F_6O_4$: C, 53.00; H, 5.62. Found: C, 53.04; H, 5.92. Compound **23**: ^1H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=0.98 (s, 3H), 1.02 (s, 3H), 1.03 (s, 3H), 1.05 (s, 3H), 1.47–1.54 (m, 1H), 1.55–1.56 (m, 2H), 1.63–1.69 (m, 1H), 1.71–1.77 (m, 1H), 1.95–2.11 (m, 5H), 4.79 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, $CDCl_3$ int): δ=19.39 (q), 25.12 (q), 29.74 (q), 29.85 (q), 34.53 (t), 36.27 (t), 38.05 (s), 40.02 (t), 40.68 (s), 43.71 (s), 46.43 (t), 50.23 (t), 87.79 (d), 114.71 (q, $^1J_{CF}$=286 Hz), 131.28 (s), 136.87 (s), 157.90 (q, $^2J_{CF}$=42 Hz); MS (EI): *m*/*z*=316 (100, M^+), 301 (23), 187 (33), 175 (34), 174 (95), 159 (44); HRMS *m*/*z* (M^+) calcd 316.1650, obsd 316.1650.

3.4. *rel*-(1*R*,2*R*,2′*S*,4*S*,7*R*)-2′,7-Dihydroxy-1,4,4′4′-tetramethyl-spiro{bicyclo[2.2.1]heptan-2,1′-cyclopentan} (24) and *rel*-(4*R*,7*S*,9*R*)-2,2,4,7-tetramethyl-1,2,3,4,5,6,7,8-octahydro-4,7-methanoazulen-9-ol (18)

The mixture of trifluoroacetates (4.40 g) obtained as described in Section 3.3 was dissolved in ether (20 mL) and added under argon with stirring to a suspension of $LiAlH_4$ (975 mg, 25 mmol) in ether (100 mL). After 2 h of reflux, TLC in pentane/ether 7:3 [R_f=0.21, 0.30 (**24**), 0.42 (**18**)] indicated that the reaction was complete. The mixture was hydrolyzed by successive addition of water (1.0 mL), 15% NaOH (1.0 mL), and water (3.0 mL). The organic layer was decanted and the residue was extracted with ether (3×50 mL). The combined organic layers were dried ($MgSO_4$) and

concentrated on a rotary evaporator (bath temperature 35 °C/15 Torr) to yield 4.30 g of a slightly yellow liquid containing 44% of **24** and 14% of **18**. 4.00 g were subjected to an acid catalyzed isomerization (see Section 3.5), and 0.30 g were used for the isolation of **18** and **24** by thick layer chromatography in pentane/ether 7:3 [SIL G-100 UV_{254}, 20×20×0.1 cm; R_f=0.30 (**24**), 0.42 (**18**)] followed by preparative GC [column B, 160 °C; retention times (min): 3.53 (**18**), 10.37 (**24**)]. Compound **18**: colorless liquid (purity 99% GC). ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.009 (s, 3H), 1.017 (s, 3H), 1.023 (s, 3H), 1.04 (s, 3H), 1.32–1.38 (m, 1H), 1.41–1.46 (m, 2H), 1.51–1.54 (m, 1H), 1.56–1.67 (m, 2H), 1.91–1.95 (m, 1H), 1.97–2.05 (m, 3H), 2.07–2.12 (m, 1H), 3.15 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, $CDCl_3$ int): δ=19.63 (q), 25.36 (q), 30.04 (q), 30.15 (q), 34.51 (t), 36.37 (t), 37.76 (s), 39.08 (t), 40.43 (s), 44.40 (s), 46.85 (t), 50.48 (t), 84.03 (d), 131.80 (s), 138.43 (s); MS (EI): *m*/*z*=220 (98, M^+), 205 (46), 191 (39), 190 (36), 189 (86), 187 (24), 175 (42), 174 (100), 163 (24), 159 (59), 150 (22), 135 (46), 121 (30), 119 (34), 107 (40), 105 (35), 95 (73), 93 (28), 91 (43), 77 (27), 55 (30), 43 (34), 41 (54). Anal. Calcd for $C_{15}H_{24}O$: C, 81.75; H. 10.98. Found: C, 81.57; H, 11.05. Compound **24**: colorless solid, mp 99 °C (purity 99% GC). ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=0.90 (s, 3H), 0.97 (s, 3H), 0.98 (s, 3H), 1.01 (s, 3H), 1.14 (ddd, *J*=12.5, 12, 6 Hz, 1H), 1.26–1.37 (m, 3H), 1.39 (dd, *J*=12.5, 3.5 Hz, 1H), 1.46 (br s, 2H), 1.52 (d, *J*=14 Hz, 1H), 1.77 (dd, *J*=12, 7 Hz, 1H), 1.83 (d, *J*=14 Hz, 1H), 1.89 (d, *J*=12.5 Hz, 1H), 3.17 (s, 1H), 4.02 (dd, *J*=10, 7 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, $CDCl_3$ int): δ=15.32 (q), 18.64 (q), 29.73 (t), 31.37 (q), 31.98 (q), 32.08 (t), 33.17 (s), 45.30 (t), 45.79 (s), 49.99 (t), 50.55 (s), 53.87 (s), 53.99 (t), 74.91 (d), 88.03 (d); MS (EI): *m*/*z*=238 (6, M^+), 220 (23), 189 (24), 152 (23), 137 (29), 123 (30), 112 (61), 111 (41), 109 (42), 107 (33), 97 (34), 95 (100), 94 (97), 85 (34), 81 (25), 71 (22), 69 (31), 55 (28), 43 (34), 41 (27). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 11.00. Found: C, 75.40; H, 10.82.

3.5. Acid catalyzed isomerization of 24: *rel*-(4*R*,7*S*,9*R*)-2,2,4,7-tetramethyl-1,2,3,4,5,6,7,8-octahydro-4,7-methano-azulen-9-ol (18)

The crude mixture of alcohols described in Section 3.4 (4.00 g) was dissolved in hexane (100 mL) and treated with 5% (w/w) H_2SO_4 on silica gel (0.05–0.20 mm) (4.70 g). The mixture was heated to 50 °C. After 24 and 27 h, more catalyst (2×2.3 g) was added, and after 46 h, the reaction was stopped. According to GC [column B, 160 °C; retention times (min): .25, 1.89, 2.46, 3.53 (**18**), 5.51, 6.09, 7.21, 8.36, 9.13, 10.37 (**24**)], at this time **24** was consumed and the content of **18** amounted to 57%. The mixture was filtered, the filtrate was washed with ether (3×50 mL), the combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL), water (2×100 mL), and dried ($MgSO_4$).The solvent was distilled off (bath temperature 35 °C/15 Torr) and the residue (2.60 g) chromatographed on silica gel (0.05–0.20 mm) in pentane/ether 7:3 (column 70×4 cm; control by GC) to yield 1.36 g (44% from **17**) of **18** as colorless liquid (purity 98%, GC). The ^{1}H and ^{13}C NMR data were identical with those given for the product in Section 3.4.

3.6. Reduction of 18

*3.6.1. With sodium in HMPA: rel-(3aR,4R,7S,8aR,9R)-2,2,4,7-tetramethyl-decahydro-4,7-methanoazulen-9-ol (**25**)*

To a solution of **18** (308 mg, 1.40 mmol) in dry HMPA (18 mL) were added at room temperature under argon with stirring small pieces of sodium (161 mg, 7.00 mmol) causing the mixture to turn blue. After 0.5, 2.0, and 3.5 h, *tert*-butanol (3×0.30 mL) was added. Afterwards the mixture was stirred overnight. The now colorless mixture was poured into water (100 mL) and extracted with pentane (3×50 mL). The extracts were washed with water (2×50 mL), dried ($MgSO_4$), and concentrated (bath temperature 30 °C/15 Torr) to yield 295 mg colorless, partly crystallizing oil. According to GC [column B, 160 °C; retention times (min): 3.78 (18), 4.81 (25)], this material contained 70 mg (23%) of unreacted **18** and 225 mg (72%) of **25**. Analytically pure **25** was obtained by preparative GC. Colorless solid, mp 71 °C. ^{1}H NMR (600 MHz, C_6D_6, C_6D_5H int): δ=0.85 (s, 3H), 0.93 (s, 3H), 0.96 (s, 3H), 0.955 (dddd, *J*=14, 13, 5, 1.5 Hz, 1H), 0.985 (d, *J*=5 Hz, 1H), 1.08 (s, 3H), 1.13 (d, *J*=14 Hz, 1H), 1.25 (ddd, *J*=13, 7, 1.5 Hz, 1H), 1.26 (dddd, *J*=13, 13, 5, 2 Hz, 1H), 1.31 (dd, *J*=14, 6 Hz, 1H), 1.34 (dd, *J*=14, 13 Hz, 1H), 1.41 (ddd, *J*=13, 11, 5 Hz, 1H), 1.52 (ddd, *J*=14, 10, 1.5 Hz, 1H), 1.58 (ddd, *J*=14, 11, 5 Hz, 1H), 1.88 (ddd, *J*=14, 10, 2 Hz, 1H), 2.19 (dddd, *J*=10, 10, 6, 1.5 Hz, 1H), 2.28 (dddd, *J*=14, 10, 10, 7 Hz, 1H), 2.89 (d, *J*=5 Hz, 1H); ^{13}C NMR (125.7 MHz, C_6D_6, C_6D_6 int): δ=25.12 (q), 26.44 (q), 27.57 (t), 29.49 (q), 29.94 (q), 32.67 (t), 34.58 (d), 35.15 (t), 37.52 (s), 40.62 (s), 41.04 (d), 42.69 (t), 44.95 (s), 49.18 (t), 83.65 (d); MS (EI): *m*/*z*=222 (6, M^+), 191 (39), 176 (46), 95 (100). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.08; H, 11.55.

*3.6.2. Through catalytic hydrogenation: rel-(3aR,4R,7S,8aR,9R)-2,2,4,7-tetramethyl-decahydro-4,7-methanoazulen-9-ol (**25**), rel-(3aR,4R,7S,8aS,9R)-2,2,4,7-tetramethyl-decahydro-4,7-methano-azulen-9-ol (**26**), and rel-(3aS,4R,7S,8aS,9R)-2,2,4,7-tetramethyl-decahydro-4,7-methanoazulen-9-ol (**10**)*

Compound **18** (48 mg, 0.22 mmol) was dissolved in acetic acid (10 mL) and hydrogenated at room temperature at 1.1 atm H_2 over PtO_2 (1.0 g) in a shaking gear. After 48 and 72 h, additional PtO_2 (2×0.50 g) was added and after 96 h the hydrogenation was stopped. According to capillary GC [30 m×0.32 mm i.d. deactivated fused-silica capillary column coated with 0.25 μm DB FFAP; 5 min 100 °C, 10 °C/min to 220 °C; 0.6 bar of H_2; retention times (min): 10.09 (**18**), 12.71 (**26**), 13.09 (**10**), 13.72 (**25**)], at this time the reaction mixture contained 20% **18**, 36% **25**, 30% **26**, and 14% **10**. The mixture was filtered, the filtrate was diluted with water (20 mL), and extracted with pentane (4×20 mL). The combined extracts were dried ($MgSO_4$) and concentrated (bath temperature 30 °C/15 Torr), and the residual oil (52 mg) was chromatographed on silica gel (0.015–0.035 mm) in pentane/ether 7:3 [column 60×2 cm; R_f=0.53 (**10**), 0.44 (**18**), 0.39 (**25**), 0.35 (**26**)] to yield pure samples of **10** (colorless liquid), **25** (colorless solid, mp 71 °C), and **26** (colorless solid, mp 79 °C). The ^{1}H and ^{13}C NMR data of **10** were identical with the literature data,[4c] and those of **25** with the data given in Section 3.6.1. Compound **26**: ^{1}H NMR (500 MHz, C_6D_6, C_6D_5H int): δ=0.90 (s, 3H), 0.95 (s, 3H), 0.96–1.11 (m, 5H), 1.04 (s, 3H), 1.05 (s, 3H), 1.16–1.24 (m, 1H), 1.29 (dd. *J*=12, 6.5 Hz, 1H), 1.31–1.37 (m, 1H), 1.38–1.50 (m, 4H), 1.83 (ddd, *J*=12, 12, 6.5 Hz, 1H), 2.87 (br s, 1H); ^{13}C NMR (75.5 MHz, C_6D_6, C_6D_6 int): δ=22.73 (q), 25.44 (q), 28.19 (t), 32.34 (q), 32.36 (q), 33.38 (t), 36.55 (s), 36.70 (t), 39.93 (d), 41.23 (t), 42.22 (s), 43.22 (s), 45.63 (d), 47.13 (t), 84.22 (d); MS (EI): *m*/*z*=222 (8, M^+), 176 (60), 175 (42), 95 (100), 81 (22), 73 (23), 61 (43), 55 (27), 45 (69), 43 (59), 41 (42); HRMS *m*/*z* (M^+) calcd 222.1984, obsd 222.1984.

3.7. *rel*-(1*S*,3*R*,5*S*)-3-(3,3-Dimethyl-cyclobutyl)-1-methyl-4-methylene-bicyclo[3.2.0]heptan-3-ol (27)

To a 1.0 M solution of lithium diisopropyl amide in hexane (120 mL, 120 mmol) was added at room temperature under argon with stirring a solution of **17** (7.3 g, 33 mmol) in THF (30 mL). The mixture was heated to 50 °C and after 1 h the reaction was complete according to TLC [pentane/ether 7:3, R_f=0.67 (**17**), 0.52 (**27**)]. The mixture was hydrolyzed with saturated aqueous ammonium chloride (40 mL), the organic layer was washed with water (3×100 mL), and dried ($MgSO_4$). The solvent was distilled off (bath temperature 35 °C/15 Torr) and the residue (7.3 g) chromatographed on silica gel (0.05–0.20 mm) in pentane/ether 7:3 (column 90×6 cm) to yield 6.9 g (94%) of **27** as colorless liquid. According to

GC [column A, 160 °C, retention time (min): 9.65], the material was 99% pure. ^{1}H NMR (600 MHz, C_6D_6, C_6D_5H int): δ=0.96 (s, 1H), 1.05 (s, 3H), 1.10 (s, 3H), 1.16 (s, 3H), 1.57–1.64 (m, 1H), 1.61 (d, J=14 Hz, 1H), 1.65–1.77 (m, 4H), 1.81 (d, J=14 Hz, 1H), 1.94 (symm m, 2H), 2.18–2.28 (m, 1H), 2.58 (pseudo quint, 1H), 2.77–2.82 (m, 1H), 4.71 (br s, 1H), 4.85 (br s, 1H); ^{13}C NMR (125.7 MHz, C_6D_6, C_6D_6 int): δ=23.45 (t), 28.01 (q), 28.93 (q), 30.30 (q), 30.33 (s), 33.21 (t), 35.50 (t), 36.11 (t), 36.36 (d), 42.52 (s), 49.77 (d), 51.47 (t), 83.97 (s), 105.76 (t), 163.43 (s); MS (EI): m/z=220 (2, M^+), 192 (34), 177 (45), 165 (50), 164 (80), 159 (27), 149 (43), 146 (29), 137 (85), 136 (83), 131 (30), 121 (81), 118 (39), 109 (100), 108 (30), 107 (34), 106 (49). Anal. Calcd for $C_{15}H_{24}O$: C, 81.75; H, 10.98. Found: C, 81.93; H, 11.00.

3.8. *rel*-(1*S*,3*R*,5*S*)-3-(3,3-Dimethyl-cyclobutyl)-3-hydroxy-5-methyl-bicyclo[3.2.0]heptan-2-one (19) and *rel*-(1*S*,2*S*)-2-[2-(3,3-dimethyl-cyclobutyl)-2-oxo-ethyl]-2-methyl-cyclobutanecarboxylic acid (28)

An ozone–oxygen mixture (1.5% w/w O_3 in O_2) was bubbled through a solution of **27** (1.50 g, 6.8 mmol) in anhydrous dichloromethane (10 mL) at −78 °C. Every 5 min the ozone–oxygen stream was stopped and the reaction progress monitored by GC [column B, 200 °C; retention times (min): 1.27 (**27**), 2.45 (**19**), 3.25, 4.05, 5.01 (**28**), 6.77]. After 20 min, **27** was consumed and the mixture contained 70% **19**, 14% **28**, and a total of 16% of three unidentified compounds. The still cold mixture was transferred to a suspension of thiourea (0.52 g, 6.8 mmol) in dichloromethane (5 mL) cooled to 0 °C and stirred for 40 min at this temperature. The mixture was filtered, the filtrate was washed with saturated aqueous sodium bicarbonate (10 mL), water (10 mL), and dried ($MgSO_4$). The solvent was distilled off (bath temperature 40 °C/15 Torr) and the residue (1.6 g) chromatographed on silica gel (0.05–0.20 mm) in pentane/ether 7:3 [column 50×2.5 cm; R_f=0.30 (**19**), 0.12 (**28**)] to yield 920 mg (60%) of **19**, mp 59 °C, and 220 mg (13%) of **28**, mp 50–52 °C, as colorless solids. According to GC, both compounds were 99% pure. Compound **19**: IR (KBr): 1729 cm^{-1} (C=O); ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.03 (s, 3H), 1.14 (s, 3H), 1.25 (s, 3H), 1.62 (symm m, 1H), 1.69–1.76 (m, 2H), 1.76 (d, J=14 Hz, 1H), 1.81 (symm m, 1H), 1.88 (pseudo t, 1H), 1.95–2.06 (m, 2H), 2.05 (d, J=14 Hz, 1H), 2.34 (br s, 1H), 2.35 (symm m, 1H), 2.59 (dd, J=11, 5.5 Hz, 1H), 2.71 (pseudo quint, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, $CDCl_3$ int): δ=18.19 (t), 28.17 (q), 28.52 (q), 30.11 (q), 30.58 (s), 33.15 (t), 34.39 (d), 34.50 (t), 34.88 (t), 37.83 (s), 47.23 (t), 49.92 (d), 82.05 (s), 221.37 (s); MS (EI): m/z=222 (17, M^+), 166 (20), 112 (22), 111 (80), 83 (66), 70 (75), 55 (100), 41 (37). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.89; H, 9.88. Compound **28**: IR (KBr): 1697 cm^{-1} (C=O); ^{1}H NMR (600 MHz, C_6D_6, C_6D_5H int): δ=0.93 (d, J=1.8 Hz, 3H), 0.96 (s, 3H), 1.26 (s, 3H), 1.56–1.67 (m, 3H), 1.70–1.78 (m, 1H), 1.94–2.02 (m, 3H), 2.17–2.25 (m, 1H), 2.47 (d, J=17 Hz, 1H), 2.57 (d, J=17 Hz, 1H), 2.67 (pseudo quint, 1H), 2.74 (pseudo t, 1H); ^{13}C NMR (125.7 MHz, C_6D_6, C_6D_6 int): δ=18.33 (t), 27.44 (q), 28.39 (q), 29.64 (q), 30.74 (t), 31.23 (s), 36.16 (t), 36.45 (t), 39.06 (d), 40.80 (s), 45.25 (t), 48.17 (d), 179.93 (s), 209.00 (s); MS (EI): m/z=238 (2, M^+), 111 (70), 83 (94), 70 (21), 56 (62), 55 (100), 41 (60). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.50; H, 9.08.

3.9. *rel*-(2a*S*,7a*S*)-5,5,7a-Trimethyl-1,2,2a,4,5,6,7,7a-octahydro-cyclobuta[*f*]inden-3-one (20)

Compound **19** (1.33 g, 6.0 mmol) was added to a 0.15 M solution of anhydrous *p*-toluenesulfonic acid in benzene (160 mL, 24.0 mmol) under argon with stirring. Afterwards the mixture was heated to 80 °C. The rearrangement was monitored by GC [column B, 200 °C; retention times (min): 1.70, 2.40 (**19**), 3.33, 3.94 (**20**)] and stopped, after the concentration of **20** had reached its maximum (7 h, 73%). The mixture was washed with saturated sodium bicarbonate (60 mL), water (2×60 mL) and dried ($MgSO_4$). The solvent was distilled off (bath temperature 30 °C/15 Torr) and the residual slightly yellow liquid (1.50 g) was chromatographed on silica gel (0.05–0.20 mm) in pentane/ether 7:3 (column 70×4 cm; control by GC) to yield 510 mg (42%) of **20** as colorless liquid (purity 97% GC). The ^{1}H and ^{13}C NMR data were in accord with the literature data.[11]

3.10. Reduction of 20

*3.10.1. Through catalytic hydrogenation: rel-(2aS,3aR,6aR,7aS)-5,5,7a-trimethyl-decahydro-cyclobuta[f]inden-3-one (**29**)*

A solution of **20** (51 mg, 0.25 mmol) in methanol (8 mL) was hydrogenated at room temperature and 1.1 atm H_2 over 10% Pd/C (200 mg) in a shaking gear until GC analysis [column B, 180 °C; retention times (min): 4.26 (**29**), 6.66 (**20**)] indicated that the reaction was complete (1.5 h). The mixture was filtered, the filtrate was diluted with water (20 mL), and extracted with pentane (4×5 mL). The combined extracts were dried ($MgSO_4$) and concentrated (bath temperature 20 °C/15 Torr) to yield 41 mg (80%) of **29** as colorless liquid (purity 95% GC). An analytically pure sample was obtained by preparative GC. IR (neat): 1710 cm^{-1} (C=O); ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=0.90 (s, 3H), 1.02 (dd, J=11, 11 Hz, 1H), 1.04 (s, 3H), 1.18 (dd, J=13, 13 Hz, 1H), 1.30 (s, 3H), 1.43 (ddd, J=13, 8, 2 Hz, 1H), 1.62 (dddd, J=12, 10, 5, 1 Hz, 1H), 1.62 (ddd, J=11, 7, 2 Hz, 1H), 1.63 (dd, J=13, 5 Hz, 1H), 1.78 (ddd, J=12, 10, 8 Hz, 1H), 1.82 (dd, J=13, 9 Hz, 1H), 2.11 (dddd, J=12.5, 10, 10, 5 Hz, 1H), 2.17 (dddd, J=12.5, 10, 8, 7 Hz, 1H), 2.58 (ddd, J=10, 7, 1 Hz, 1H), 2.77 (ddd, J=12, 9, 8 Hz, 1H), 2.89 (ddddd, J=13, 12, 11, 7, 5 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, $CDCl_3$ int): δ=17.62 (t), 26.76 (q), 27.29 (q), 28.76 (q), 32.59 (t), 38.29 (s), 39.05 (t), 40.14 (d), 41.16 (t), 43.84 (s), 48.29 (d), 48.52 (t), 50.60 (d), 218.24 (s); MS (EI): m/z=206 (37, M^+), 191 (54), 178 (68), 163 (22), 122 (30), 109 (20), 82 (100), 81 (25), 67 (22), 55 (26); HRMS m/z (M^+) calcd 206.1671, obsd 206.1671.

*3.10.2. With lithium in liquid ammonia: rel-(2aS,3aR,6aR,7aS)-5,5,7a-trimethyl-decahydro-cyclobuta[f]inden-3-one (**29**), rel-(2aS,3aR,6aS,7aS)-5,5,7a-trimethyl-decahydro-cyclobuta[f]inden-3-one (**30**), and rel-(2aS,3aS,6aS,7aS)-5,5,7a-trimethyl-decahydro-cyclobuta[f]inden-3-one (**21**)*

To a solution of lithium (42 mg, 6.0 mmol) in liquid ammonia (60 mL) was added at −78 °C under argon with stirring a solution of **20** (409 mg, 2.0 mmol) in anhydrous ether (20 mL). After 30 min at −78 °C the ammonia was allowed to evaporate. The residue was diluted with ether (40 mL) and hydrolyzed by careful addition of saturated aqueous ammonium chloride (10 mL). The layers were separated, the aqueous layer was extracted with pentane (40 mL), and the combined organic layers were washed with water (3×40 mL) and dried ($MgSO_4$). Most of the solvents were distilled off over a 20 cm vigreux column and last traces were eliminated in vacuo (bath temperature 30 °C/15 Torr). According to GC [column A, 180 °C; retention times (min): 7.67 (**30**), 8.31 (**29**), 9.73 (**21**), 12.58 (**20**); column B, 180 °C; retention times (min): 4.42 (**29**, **30**), 5.48 (**21**), 6.94 (**20**)], the residue (410 mg) contained still 40% of **20**. Therefore, a second reduction with lithium (69 mg, 10 mmol) in liquid ammonia (100 mL) under the same conditions was performed. The material thus obtained (408 mg) contained 15% **20**, 19% **29**, 13% **30**, and 53% **21** and was chromatographed on silica gel (0.05–0.20 mm) in pentane/ether 9:1 [column 50×2.5 cm; R_f=0.33 (**29**, **30**), 0.27 (**21**), 0.10 (**20**); control by GC] to yield 46 mg (11%) of a mixture of **29** and **30** as colorless liquid, and 144 mg (34%) of pure **21** as colorless solid, mp 155–157 °C. Pure **30** was obtained by acid catalyzed epimerization of **21** to give a separable 7:3 mixture of **21** and **30** (see Section 3.11). We observed this epimerization even in $CDCl_3$. Therefore all spectra were taken in C_6D_6. Compound **21**:

^{1}H NMR (600 MHz, C_6D_6, C_6D_5H int): δ=0.70 (dd, J=13, 13 Hz, 1H), 0.925 (dd, J=13, 8 Hz, 1H), 0.93 (s, 3H), 1.27 (dd, J=13, 5 Hz, 1H), 1.50–1.57 (m, 1H), 1.60 (ddd, J=13, 8, 2 Hz, 1H), 1.64–1.70 (m, 2H), 1.80–1.92 (m, 3H), 2.66 (dd, J=10, 6.5 Hz, 1H), 2.68–2.76 (m, 1H), 2.99 (ddd, J=11, 11, 8 Hz, 1H); ^{13}C NMR (125.7 MHz, C_6D_6, C_6D_6 int): δ=16.80 (t), 27.36 (q), 28.17 (t), 28.92 (q), 29.94 (q), 36.99 (d), 37.68 (s), 40.86 (t), 41.55 (s), 42.24 (t), 47.38 (d), 48.99 (t), 52.36 (d), 214.43 (s). For data in $CDCl_3$, see Ref. 3m.

3.11. Acid catalyzed equilibration of 21: *rel*-(2a*S*,3a*R*,6a*S*,7a*S*)-5,5,7a-trimethyl-decahydro-cyclobuta[*f*]inden-3-one (30)

To a solution of pure **21** (85 mg, 0.41 mmol) in benzene (3.0 mL) was added Nafion NR 50 (beads, 10–35 mesh, 200 mg) and the mixture stirred at room temperature. According to GC [column B; 180 °C; retention times (min): 4.50 (**30**), 5.49 (**21**)], after 1 h the equilibration to a 7:3 mixture of **21** and **30** was complete. Pure **30** was obtained by preparative GC. Colorless liquid. ^{1}H NMR (600 MHz, C_6D_6, C_6D_5H int): δ=0.83 (dd, J=13, 12 Hz, 1H), 0.92 (dd, J=12, 11 Hz, 1H), 0.95 (s, 3H), 0.96 (s, 3H), 1.08 (s, 3H), 1.19–1.24 (m, 1H), 1.32 (dd, J=13, 3.5 Hz, 1H), 1.46 (dd, J=12, 6.5 Hz, 1H), 1.485 (dd, J=13, 7.5 Hz, 1H), 1.76–1.83 (m, 2H), 1.84–1.96 (m, 1H), 1.98 (dd, J=13, 10 Hz, 1H), 2.03–2.13 (m, 2H), 2.28–2.32 (m, 1H); ^{13}C NMR (125.7 MHz, C_6D_6, C_6D_6 int): δ=20.28 (t), 29.34 (q), 30.54 (t), 31.64 (q), 32.06 (q), 37.03 (s), 38.88 (t), 42.90 (t), 43.39 (d), 44.32 (s), 48.94 (t), 52.08 (d), 56.73 (d), 211.90 (s). For data in $CDCl_3$, see Refs. 3i,n.

3.12. (+)-(*SS*,1*S*,3*R*,4*S*,5*R*)-3-(*N*-Methyl-*S*-phenyl-sulfonimidoylmethyl)-1,4-dimethyl-bicyclo-[3.2.0]heptan-3-ol [(+)-(*SS*,1*S*,3*R*,4*S*,5*R*)-(31)]

To a solution of (*S*)-(+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine[16c–e] (1.28 g, 7.5 mmol, $[\alpha]_D^{20}$ +183 (*c* 1.64, acetone), >99% ee[17]) in anhydrous THF (22.5 mL) was added at 0 °C under argon with stirring a 1.6 M solution of *n*-butyllithium in hexane (4.7 mL, 7.5 mmol). Afterwards the mixture was stirred for 15 min at room temperature until it was cooled to −78 °C. A solution of (±)-**13**[4c] (690 mg, 5.0 mmol) in anhydrous THF (2.5 mL) was added and the reaction progress monitored by TLC [pentane/ether 7:3; R_f=0.53 (**13**), 0.24 (**31**), 0.14 (3 diastereoisomers)]. After 1.5 h at −78 °C no further change was observed. The mixture was hydrolyzed with saturated aqueous ammonium chloride (2.0 mL), the aqueous layer was discarded, and the organic layer was dried ($MgSO_4$) and concentrated (bath temperature 35 °C/15 Torr). The residue (2.0 g) was chromatographed on silica gel (0.05–0.20 mm) in pentane/ether 7:3 (column 65×3.5 cm) to yield 590 mg (76%) of pure (+)-**31** as colorless solid, mp 150–152 °C (purity 99% ^{1}H/^{13}C). As derived from (*S*)-(+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (>99% ee), (+)-**31** was enantiomerically pure (>99% ee). A second eluted crop of 500 mg (64%) contained 20% (+)-**31** and 80% of a 7:2:1 mixture of three diastereoisomers (^{13}C NMR) and was discarded. Compound (+)-**31**: ^{1}H NMR (600 MHz, C_6D_6, C_6D_5H int): δ=1.00 (d, J=7 Hz, 3H), 1.20 (s, 3H), 1.39 (dq, J=7, 7 Hz, 1H), 1.86–1.94 (m, 2H), 2.08 (d, J=14 Hz, 1H), 2.15–2.20 (m, 1H), 2.35 (d, J=13 Hz, 1H), 2.49–2.54 (m, 1H), 2.53 (s, 3H), 2.56–2.61 (m, 1H), 2.86 (d, J=14 Hz, 1H), 3.32 (d, J=13 Hz, 1H), 6.70 (s, 1H), 6.95–7.01 (m, 3H), 7.64–7.67 (m, 2H); ^{13}C NMR (125.7 MHz, C_6D_6, C_6D_6 int): δ=8.40 (q), 15.23 (t), 28.62 (q), 28.92 (q), 31.54 (t), 43.60 (s), 48.65 (d), 48.72 (d), 53.53 (t), 64.97 (t), 83.01 (s), 129.26 (d), 129.46 (d), 132.64 (d), 139.84 (s); MS (EI): m/z=308 (2, $[M+H]^+$), 252 (45), 156 (100), 125 (98), 107 (66); MS (DCI): m/z=308 (100, $[M+H]^+$). $[\alpha]^{20}$ (nm) +88.3 (589), +92.2 (578), +105.7 (546), +187.7 (436), +313.9 (365) (*c* 1.22, $CHCl_3$). Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20. Found: C, 66.54; H, 7.94.

3.13. (+)-(1*S*,4*S*,5*R*)-1,4-Dimethyl-bicyclo[3.2.0]heptan-3-one [(+)-(1*S*,4*S*,5*R*)-(13)]

Compound (+)-**31** (2.16 g, 7.0 mmol) was heated under argon to 140 °C. According to TLC [pentane/ether 7:3; R_f=0.53 ((+)-**13**), 0.24 (**31**)], after 4 h the reaction was complete. The resulting mixture was chromatographed on silica gel (0.05–0.20 mm) in pentane/ether 7:3 (column 70×4 cm) yielding 770 mg (89%) of (+)-**13** as colorless liquid (purity 99%). The chemical purity was determined by GC [column B, 160 °C; retention time (min): 1.69 ((+)-**13**)]. As derived from (+)-**31** (>99% ee), (+)-**13** was enantiomerically pure (>99% ee). $[\alpha]^{20}$ (nm) +78.7 (589), +82.7 (578), +95.0 (546), +177.3 (436), +318.9 (365) (*c* 1.41, acetone). The ^{1}H and ^{13}C NMR data were identical with those of (±)-**13**.[4c]

3.14. (+)-(1*S*,3*S*,4*S*,5*R*)-3-(3,3-Dimethyl-cyclobutyl)-1,4-dimethyl-bicyclo[3.2.0]heptan-3-ol [(+)-(1*S*,3*S*,4*S*,5*R*)-(32)]

The addition of 3,3-dimethyl-cyclobutylmagnesium bromide to (+)-**13** (690 mg, 5.0 mmol) was performed as described for (±)-**13**[4c] and yielded 1.75 g (78%) of (+)-**32** as colorless oil (purity 99%). The chemical purity was determined by GC [column A, 200 °C; retention time (min): 3.91 ((+)-**32**)]. As derived from (+)-**13** (>99% ee), (+)-**32** was enantiomerically pure (>99% ee). $[\alpha]^{20}$ (nm) +22.9 (589), +23.7 (578), +26.8 (546), +43.0 (436), +62.8 (365) (*c* 1.39, acetone). The ^{1}H and ^{13}C NMR data were identical with those of (±)-**32**.[4c]

3.15. (−)-(1*R*,2*S*,4*S*,7*R*)-2-(3,3-Dimethyl-cyclobutyl)-1,4-dimethyl-bicyclo[2.2.1]heptan-7-ol [(−)-(1*R*,2*S*,4*S*,7*R*)-(15)], (+)-(1*R*,2*R*,4*S*,7*R*)-2-(3,3-dimethyl-cyclobutyl)-1,4-dimethyl-bicyclo[2.2.1]heptan-7-ol [(+)-(1*R*,2*R*,4*S*,7*R*)-(16)], and (+)-(3a*S*,4*R*,7*S*,8a*S*,9*R*)-2,2,4,7-tetramethyl-decahydro-4,7-methanoazulen-9-ol [(+)-(3a*S*,4*R*,7*S*,8a*S*,9*R*)-(10)]

The rearrangement of (+)-**32** (667 mg, 3.00 mmol) with trifluoroacetic acid, the subsequent reduction with lithium aluminum hydride, and the purification of the resulting alcohols (614 mg) were performed as described for (±)-**32**[4c] and yielded (−)-**15** (purity 99%), (+)-**16** (purity 99%), and (+)-**10** (purity 99%). The chemical purities were determined by GC {column A, 180 °C; retention times (min): 10.83 [(+)-**16**], 11.43 [(−)-**15**], 15.01 [(+)-**10**]}. As derived from (+)-**32** (>99% ee), all compounds were enantiomerically pure (>99% ee). The optical rotations were as follows: compound (−)-**15**: $[\alpha]^{20}$ (nm) −33.8 (589), −35.3 (578), −40.2 (546), −69.9 (436), −112.8 (365) (*c* 1.35, acetone); compound (+)-**16**: $[\alpha]^{20}$ (nm) +75.5 (589), +78.8 (578), +89.6 (546), +152.2 (436), +238.2 (365) (*c* 1.36, acetone); compound (+)-**10**: $[\alpha]^{20}$ (nm) +25.2 (589), +26.3 (578), +30.0 (546), +49.9 (436), +73.9 (365) (*c* 1.00, $CHCl_3$). The ^{1}H and ^{13}C NMR data were identical with those previously reported.[4c]

3.16. X-ray analyses of *rel*-(1*S*,3*R*,5*S*)-19, *rel*-(3a*R*,4*R*,7*S*,8a*S*,9*R*)-26, and (+)-(*SS*,1*S*,3*R*,4*S*,5*R*)-31

X-ray data were collected on a Stoe IPDSII diffractometer at 200 K (**19**, **26**) and on a Stoe four-circle diffractometer equipped with a Bruker CCD camera at 273 K (**31**), respectively, using graphite-monochromated Mo Kα radiation (λ=0.71073 Å). The structures were solved by using direct methods with SHELX-97 and refined by full-matrix least-squares on F^2 for all data with SHELX-97.[18] All non-hydrogen atoms were refined anisotropically. A riding model with idealized geometry was employed for all hydrogen atoms. The crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 705776 (**19**), 705777 (**26**), and 705778 (**31**). Copies of the data can be obtained, free of charge,

on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary data

^{1}H and ^{13}C NMR spectra of **17**–**19**, **21**–**31**, and data of the X-ray analyses including ORTEP plots of **19**, **26**, and **31** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.066.

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