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TETRAHEDRON

A REARRANGEMENT APPROACH TO (±)-CERAPICOL[1]

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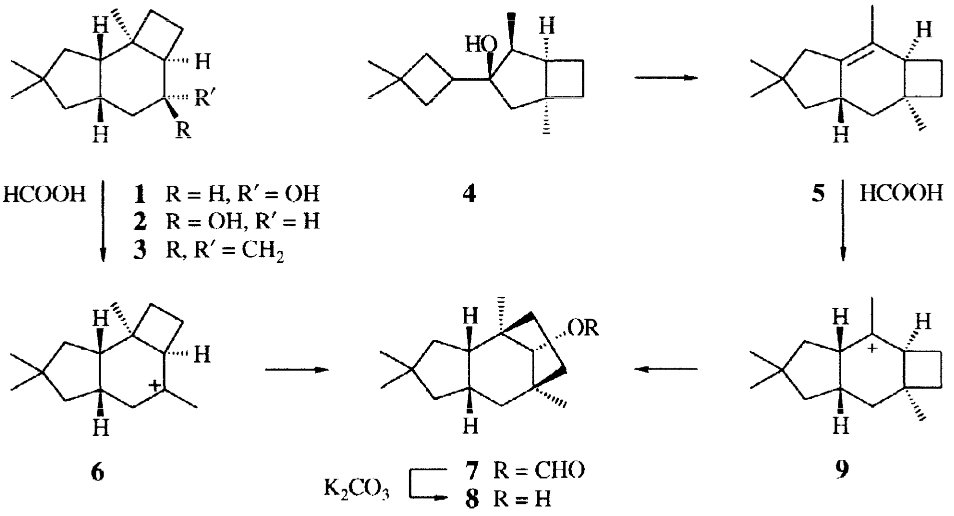
Abstract: The synthesis and rearrangement of the cyclobutyl methanol **4** is described. The synthesis has been achieved by addition of the Grignard reagent **16** to the bicyclic ketone **22**. Experimental procedures for the preparation of both compounds are given. Upon treatment with trifluoroacetic acid and subsequent reduction, **4** yields the norbornanes **24** and **25** and (±)-cerapicol (**8**). Some consequences concerning the search for other potential precursors of **8** are discussed. © 1999 Elsevier Science Ltd. All rights reserved.

In 1988, Hanssen and Abraham[2] isolated a novel tricyclic protoilludane sesquiterpene alcohol as a metabolite of the fungus *ceratocystis picea* cultured on solid media and named it (−)-cerapicol (**8**). Interestingly, the same alcohol, albeit in racemic form, had already been obtained twelve years before through formolysis of the protoilludyl cation equivalents **1-3** and subsequent saponification [**1**(**2**,**3**)-**6**-**7**-**8**].[3] Since then, no synthesis of **8** has been reported.



Given the fact that the formate **7** may also be obtained by formolysis of the protoilludane sesquiterpene (±)-sterpurene (**5**) via cation **9**,[4] the cyclobutyl methanol **4** was thought to be a suitable candidate for a rearrangement to **8** via an initial twofold ring enlargement with transient formation of **5**. The present communication describes its synthesis and details the results of its acid catalyzed rearrangement.

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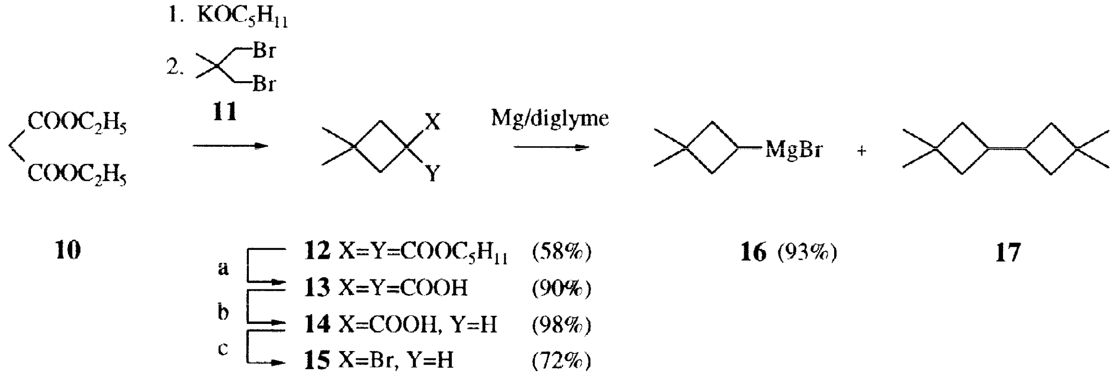
For the synthesis of **4**, we envisaged an addition of 3,3-dimethyl-cyclobutylmagnesium bromide (**16**)[5,6] to the bicyclic ketone **22**.[7,8] For the preparation of **16**, we adopted the procedure of Roberts[5] and reacted malonic acid diethyl ester (**10**) with potassium pentanolate and 1,3-dibromo-2,2-dimethyl-propane (**11**)[9] to give the dipentyl ester **12**. After saponification, the resulting dicarboxylic acid **13** was decarboxylated and subjected to a Hunsdiecker degradation[10] to give the required cyclobutyl bromide **15** (**13**-**14**-**15**). As recommended by Fraenkel,[6] the subsequent Grignard reaction to **16** was run in diglyme. In tetrahydrofuran [5] or ether, extensive coupling to **17** was observed.



10

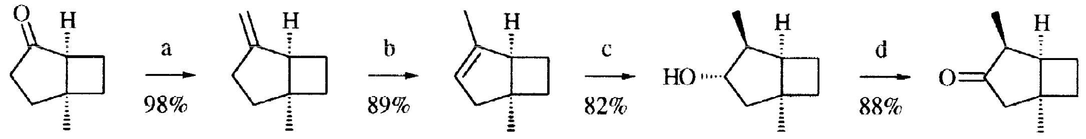
12 X=Y=$COOC_5H_{11}$ (58%)
13 X=Y=COOH (90%)
14 X=COOH, Y=H (98%)
15 X=Br, Y=H (72%)

16 (93%)

17

(a) (1) $KOH/EtOH/H_2O$/4h/rflx, (2) HCl, (b) 2.5h/200°C
(c) (1) $KOH/AgNO_3$, (2) Br_2/CCl_4/1.5h/-25°C/-5°C

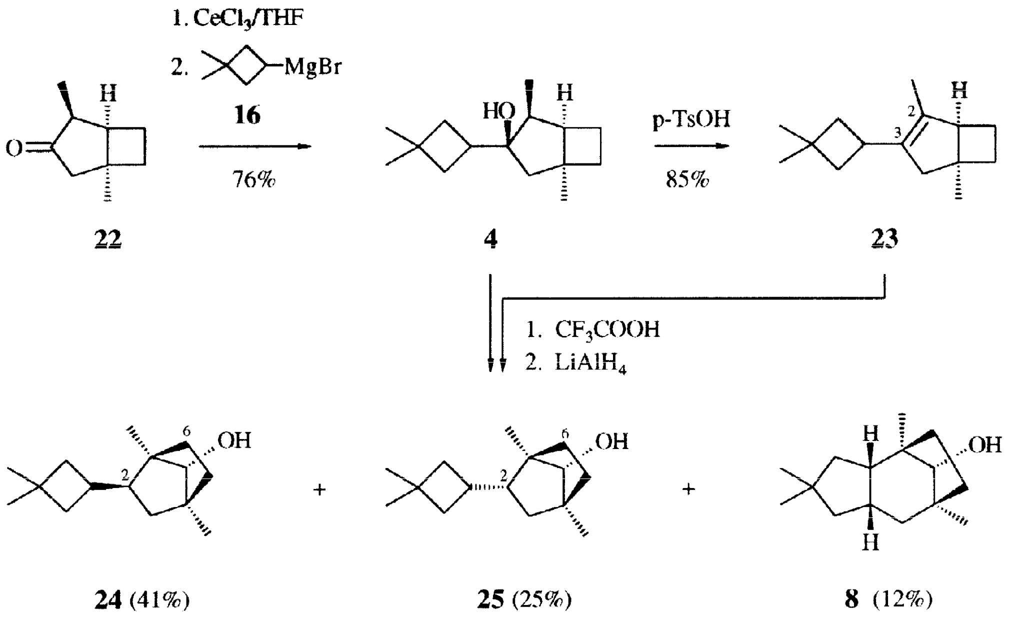
For the preparation of **22**, the bicyclic ketone **18**[11] was first methylenated to **19**,[12] then isomerized to **20**,[13] and finally hydroborated to **21** and oxidized to **22**[14] using standard reagents and procedures. This sequence via a new and efficient entry to **20** compares favourably with those reported.[7,8]



18 **19** **20** **21** **22**

(a) $Ph_3P{=}CH_2$/1h/40°C, (b) t-BuOK/DMSO/3h/80°C
(c) (1) BH_3/THF/1h/rt, (2) $NaOH/H_2O_2$/1h/rt, (d) PCC/CH_2Cl_2/1h/rt

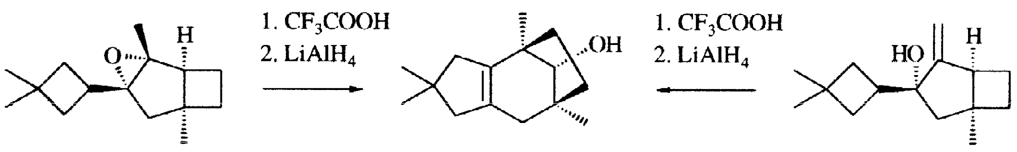
When **22** was subjected to a $CeCl_3$ catalyzed addition[15] of the Grignard reagent **16**, a single addition product was formed. Assuming a preferential exo-attack of the reagent, we formulate this product as **4**. To our disappointment, treatment of **4** with p-toluenesulfonic acid in benzene did not provoke any rearrangement. An undesired elimination with subsequent isomerization, delivering the tetrasubstituted olefin **23** as thermodynamically most stable isomer[16] of originally three olefins was observed instead.



At this stage it became clear, that a rearrangement of **4** could only be enforced by stronger acids, and that the outcome was unpredictable because of the unknown regio- and stereochemistry of the protonation of the initially formed **23** and the unknown barriers for the ring enlargements which had to follow. Indeed, it was only with trifluroacetic acid, that an instantaneous rearrangement of both **4** and **23** took place, leading to identical mixtures of trifluoroacetates, and, after reduction with lithium aluminium hydride, to identical mixtures of alcohols. These mixtures contained the stereoisomeric norbornanes **24** (41%) and **25** (25%) and the desired (±)-cerapicol (**8**) (12%). Albeit a separation proved difficult, it could finally be achieved by a combination of column and gas chromatography.

Of the products formed, (±)-cerapicol (**8**) was identified by means of its known ^{1}H NMR data in deuterochloroform.[2] To achieve a better separation of overlapping signals and to generate a full data set we performed additional high-field ^{1}H NMR, ^{13}C NMR, APT, HETCOR, COSY and NOESY measurements in deuterobenzene. These measurements allowed a full assignment of all ^{1}H, and, for the first time, of all ^{13}C NMR resonances. Details are given in the experimental part. The same technique as with **8** was applied to elucidate the structure and stereochemistry of **24**, and once again, a full assignment proved possible. With the ^{13}C NMR data of **24** at hand, the structure of **25** followed from a large upfield shift of C-6 [δ = 36.20 (**25**) vs 27.55 (**24**)], characteristic for 2-exo substitued norbornanes.[17] The same conclusion could be drawn from a comparision of the mass spectra. In both cases, the dominating fragmentation was an extrusion of 1,1-dimethyl-3-vinylcyclobutane leading from the molecular ion (m/z = 222) to the basic ion (m/z = 112). This result confirms that **24** and **25** differ only in the stereochemistry at C-2.

Of the products observed, the norbornanes **24** and **25** must have been formed by a protonation of C-3 of **23** from the exo and endo side, respectively, followed by a bicyclo[3.2.0]oct-2-yl to bicyclo[2.2.1]oct-7-yl rearrangement and a backside attack of the trifluroacetoxy anion. An analogous rearrangement of **19** is known.[12] The mechanism of the formation of (±)-cerapicol (**8**) is less obvious. However, assuming that C-2 of **23** is protonated preferentially from the exo side, we believe that the initial C_4-C_5 and C_5-C_6 ring enlargements are followed by an elimination and a reprotonation adjusting the stereochemistry of the bridge. If not, stereoisomers of **8** should have been formed.



In any case, it is clear from the above that the monofunctional cyclobutyl methanol **4** is an unsuitable precursor for a productive synthesis of (±)-cerapicol (**8**). However, the situation may change if (potentially) difunctional derivates as the epoxide **26** and/or the allylic alcohol **28** are employed. In these cases, a ring enlargement of the cyclobutyl substituent should not be inhibited, even if the 1,3-bridge is formed first. It could therefore well be that both compounds rearrange to **27** as another potential precursors of **8** and stabilomer[18] of a series of seven isomeric olefins. Research following these lines is in progress.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Varian VXR 200, VXR 500 or a Bruker AMX 300 spectrometer. For standards other than TMS the following chemical shifts were used: $\delta_H(CHCl_3) = 7.24$, $\delta_H(C_6D_5H) = 7.15$, δ_H $(CD_2HOD) = 3.30$, $\delta_C(CDCl_3) = 77.00$, $\delta_C(C_6D_6) = 128.00$, $\delta_C(CD_3OD) = 49.00$. Mass spectra were obtained with a Varian MAT 311A, Varian MAT 731, or a Finnigan MAT 95 instrument operated at 70 eV.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. Product ratios were not corrected for relative response. R_f values are quoted for Macherey & Nagel Polygram SIL G/UV_{254} plates. Colourless substances were detected by oxidation with 3.5% alcoholic 12-molybdophosphoric acid (Merck) and subsequent warming. Boiling and melting points are not corrected. For the preparation of anhydrous $CeCl_3$, finely powdered $CeCl_3 \cdot 7H_2O$ was heated at 140°C/0.1 torr to constant weight.

3,3-Dimethyl-cyclobutane-1,1-dicarboxylic acid dipentyl ester (12): To a solution of potassium pentanolate in pentanol, prepared from potassium (71.0 g, 1.82 mol) and absolute pentanol (900 ml), was added under nitrogen with stirring, first, within 15 min at 70°C malonic acid diethyl ester (182 g, 1.14 mol), and second, within 1.5 h at 130°C 1,3-dibromo-2,2-dimethylpropane (**11**)[9] (205 g, 0.89 mol). After the addition was complete, the reaction mixture was heated for 4h to 130°C until most of the solvent was distilled off at ordinary pressure and the cold residue was treated with water (300 ml). The phases were separated, the aqueous phase was extracted with ether (3 x 100 ml), the combined organic phases were dried ($MgSO_4$), the solvents were distilled off and the residue was fractionated to yield 140 g (58%) of **12** as colourless liquid, bp 120°C/0.1 torr. ^1H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int): δ = 0.87 (t, 6, J = 8 Hz), 1.10 (s, 6), 1.20-1.36 (m, 8), 1.54-1.68 (m, 4), 2.35 (s, 4), 4.10 (t, 4, J = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, $CHCl_3$ int): δ = 13.88 (q), 22.21 (t), 27.91 (t), 28.16 (t), 29.45 (q), 30.08 (s), 41.25 (t), 46.46 (s), 65.47 (t), 172.45 (s).

3,3-Dimethyl-cyclobutane-1,1-dicarboxylic acid (13): To a solution of potassium hydroxide (131g, 2.34 mol) in ethanol (350 ml) and water (175 ml) was added **12** (210 g, 0.67 mol) and the mixture was heated 4h to reflux. The ethanol and the liberated pentanol were distilled off as azeotropic mixtures with water (ethanol/water 96:4, bp 78.2°C; pentanol/water 45:55, bp 95.4°C) and the residue was acidified with concentrated hydrochloric acid to pH=1 (250 ml). The resulting suspension was perforated for 4h with ether, and the etheral extract concentrated to yield 104 g (90%) of **13** as colourless solid, mp 173°C (decomp) [lit.[19] mp 162°C (decomp)]. ^1H NMR (300 MHz, CD_3OD, CHD_2OD int): δ = 1.12 (s, 6), 2.35 (s, 4), 4.90 (br s, 2); ^{13}C NMR (75 MHz, CD_3OD, CD_3OD int): δ = 29.91 (q), 30.83 (s), 42.39 (t), 47.38 (s), 175.87 (s).

3,3-Dimethyl-cyclobutane carbocylic acid (14): **13** (103 g, 0.60 mol) was heated to 200°C until the gas evolution had been ceased (2.5 h). Subsequent distillation yielded 64 g (83%) of **14** as colourless, unpleasant smelling liquid, bp 127-129°C/30 torr (lit.[19] bp 105-106°C/15 torr). ^1H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int): δ = 1.08 (s, 3), 1.12 (s, 3), 1.90-2.12 (m, 4), 3.07 (quint, 1, J = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, $CDCl_3$ int): δ = 28.25 (q), 29.99 (q), 31.43 (d), 32.03 (s), 37.52 (t), 182.77 (s).

3-Bromo-1,1-dimethyl-cyclobutane (15): A solution of **14** (32 g, 0.25 mol) in water (70 ml) was neutralized with aqueous potassium hydroxide (2N, 125 ml) until a solution of silver nitrate (43 g, 0.25 mol) in water (140 ml) was added with stirring. After 30 min, the precipitated white-grey silver salt was filtered, washed with water (200 ml), methanol (200 ml) and dried (48 h/60°C/0.01 torr). The yield from two identical preparations amounted to 114 g (97%). For the Hunsdiecker degradation, the silver salt (37.6 g, 0.16 mol) was added portionwise within 15 min at -25°C to a solution of bromine (25.6 g, 0.16 mol) in tetrachloromethane (200 ml). After the mixture had become colorless (30 min), it was allowed to warm up to -5°C and was held there until the gas evolution had ceased (1.5 h). The precipitated silver bromide was filtered off and washed with tetrachloromethane (2 x 50 ml), and the combined filtrates were washed with aqueous sodium hydroxide (2N, 2 x 100 ml), water (2 x 100 ml) and dried ($MgSO_4$). The solvent was distilled over a 30 cm Vigreux column and the residue was fractionated to give pure **15** as colourless liquid, bp 133°C (lit.[5] bp 132°C). The yield from three runs amounted to 58.4 g (72%).^1H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int): δ = 1.10 (s, 3), 1.20 (s, 3), 2.24-2.36 (m, 2), 2.40-2.52 (m, 2), 4.46 (quint, 1, J = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, $CDCl_3$ int): δ = 27.55 (q), 31.05 (q), 33.82 (s), 38.47 (d), 47.93 (t).

3,3-Dimethyl-cyclobutylmagnesium bromide (16) and 3,3,3′,3′-Tetramethyl-bicyclobutyl (17): Mg turnings (3.50 g, 144 mmol) and a few crystals of I_2 were covered with diglyme (40 ml), and a portion of the full amount of **15** (11.7 g, 72 mmol) was added at 50°C under argon with stirring. The reaction was started by addition of a few drops of methyl iodide until the rest of **15** was added within 30 min at 50°C. After additional 2 h at the same temperature, tituration of an aliquot indicated that the solution was 1.36 M (93%). GC analysis [3 m x 1/4″ all glass system, 15% OV 101 on Chromosorb W AW/DMCS, 60/80 mesh, 5 min 80°C, 20°C/min to 220°C; retention times (min): 6.9 (**15**), 9.8 (**17**)] revealed that **15** had been completely consumed and that a small amount of **17** had been formed. An pure sample was obtained by preparative GC. Colorless liquid. ^1H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int): δ = 1.00 (s, 6), 1.10 (s, 6), 1.30-1.40 (m, 4), 1.62-1.72 (m, 4), 2.08-2.26 (m, 2); ^{13}C NMR (75 MHz, $CDCl_3$, $CDCl_3$ int): δ = 28.97 (q), 30.73 (s), 30.94 (q), 33.08 (d), 37.94 (t); MS m/z 166 (1, M^+), 56 (100). Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.33. Found: C, 86.86; H, 13.12.

(1*SR*,5*RS*)-1-Methyl-4-methylene-bicyclo[3.2.0]heptane (19): To a stirred suspension of potassium-t-butoxide (28.0 g, 250 mmol) in ether (500 ml) under argon was added methyltriphenylphosphonium bromide (89.2 g, 250 mmol) and the mixture heated to reflux. After 30 min, most of the solvent was distilled off until the internal temperature reached 40°C. **18**[11] (21.1 g, 170 mmol) was added dropwise, and, after the exothermic reaction had subsided, the mixture was heated for 1h to reflux. The mixture was hydrolyzed with water (20 ml), the residue was extracted with pentane (3 x 100 ml) and the combined organic phases were washed with water (3 x 100 ml) and dried (MgSO$_4$). The solvents were distilled over a 60 cm Vigreux column with occasional filtration from separated triphenylphosphine oxide, and the residue was fractionated to yield 20.4 g (98%) of a colourless liquid, bp 130-135°C (lit.[12] 60°C/60 torr), consisting of a 83:17-mixture of **19** and **20** according to GC [3 m x 1/4″ all glass system, 15% FFAP on Chromosorb W AW/DMCS, 60/80 mesh, 80°C; retention times (min): 2.8 (**20**), 3.2 (**19**)]. This material was used for the subsequent isomerization. The ^{1}NMR data of **19** were in accord with literature data.[12] The ^{13}C NMR data (50 MHz, CDCl$_3$, CDCl$_3$ int) have not yet been reported and were as follows: δ = 22.01 (t), 26.46 (q), 30.15 (t), 33.66 (t), 40.20 (t), 45.77 (s), 48.63 (d), 104.22 (t), 158.33 (s).

(1*RS*,5*RS*)-2,5-Dimethyl-bicyclo[3.2.0]hept-2-ene (20): To a solution of potassium-t-butoxide (9.0 g, 80 mmol) in DMSO (80 ml) was added under argon with stirring a 83:17-mixture of **19** and **20** (20.1 g, 165 mmol) and the resulting two-phase mixture heated for 3 h to 80°C. The mixture was diluted with water (300 ml) and extracted with pentane (1 x 200 ml, 2 x 100 ml), and the combined extracts were washed with water (3 x 100 ml) and dried (MgSO$_4$). The solvent was distilled off over a 60 cm Vigreux column and the residue was fractionated to yield 17.9 g (89%) of pure **20** as colorless liquid, bp 135°C (lit.[7] 130-137°C). The ^{1}H and ^{13}C NMR data were in accord with literature data.[8]

(1*SR*,3*SR*,4*SR*,5*RS*)-1,4-Dimethyl-bicyclo[3.2.0]heptan-3-ol (21): To a solution of **20** (17.1 g, 140 mmol) in THF (50 ml) was added under argon with stirring a 1 M solution of borane in THF (140 ml, 140 mmol) causing a slightly exothermic effect. After the addition was complete, the mixture was stirred for 1 h at room temperature until water (35 ml), aqueous sodium hydroxide (3N, 40 ml) and hydrogen peroxide (30%, 30 ml) were successively added such that the internal temperature did not exceed 50°C. After 1 h at room temperature the mixture was diluted with ether (250 ml) and washed with water (2 x 100 ml) and saturated ammonium chloride (2 x 100 ml). The combined aqueous phases were extracted with ether (150 ml), the extract was washed with water (2 x 50 ml) and saturated ammonium chloride (2 x 50 ml), and the organic phases were combined and dried (MgSO$_4$). The solvents were distilled off over a 60 cm Vigreux column and the residue fractionated in vacuo to yield 16.1 g (82%) of **21** as colorless viscous liquid, bp 91-93°C/15 torr. The ^{1}H and ^{13}C NMR data were in accord with literature data.[8]

(1*SR*,4*SR*,5*RS*)-1,4-Dimethyl-bicyclo[3.2.0]heptan-3-one (22): To a suspension of pyridinium chlorochromate (35.6 g, 165 mmol) in dichloromethane (220 ml) was added under argon with stirring a solution of **21** (15.4 g, 110 mmol) causing an exothermic effect and the separation of a black grease. After 1.5 h, the supernatant liquid was poured into ether (1 l), the residual grease was extracted with ether (2 x 100 ml), and the combined etheral phases were filtered over silica gel (0.05-0.20 mm, column 25 x 5 cm) and eluted with ether (300 ml). The solvents were distilled off over a 60 cm Vigreux column and the residue fractionated in vacuo to yield 13.4 g (88%) of **22** as colourless liquid, bp 74-76°C/16 torr. The ^{1}H and ^{13}C NMR data were in accord with literature data.[8]

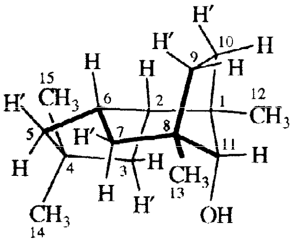
(1*SR*,3*SR*,4*SR*,5*RS*)-3-(3,3-Dimethyl-cyclobutyl)-1,4-dimethyl-bicyclo[3.2.0]heptan-3-ol (4): A suspension of finely powdered dry CeCl$_3$ (9.20 g, 37.5 mmol) in THF (140 ml) was stirred for 2 h at room temperature. A solution of **22** (2.07 g, 15.0 mmol) in THF (20 ml) was added, and after additional 2 h of stirring the mixture was cooled to 0°C until a 1.36 M solution of **16** in ether (22 ml, 30 mmol) was added dropwise. After 15 min at 0°C and 30 min at room temperature the reaction was complete according to GC [3 m x 1/4″ all glass system, 15% FFAP on Chromosorb W AW/DMCS, 60/80 mesh, 5 min 160°C, 30°C/min to

230°C, 5 min 230°C; retention times (min): 3.1 (**22**), 7.8 (**4**)]. The mixture was hydrolyzed with saturated ammonium chloride (20 ml), the organic phase was decanted, the residue was washed with ether (2 x 50 ml), and the combined organic phases were dried ($MgSO_4$). Most of the solvents were distilled off (bath temperature up to 120°C/60 torr) and the residue (5.20 g yellow oil) chromatographed on silica gel (0.05-0.20 mm) in pentane/ether [9:1, column 80 x 5 cm; $R_f = 0.42$ (**4**)] to yield 2.52 g (76%) of **4** as colourless oil (purity 97% GC). An analytically pure sample was obtained by preparative GC. ^1H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int): δ = 0.82 (d, 3, J = 7 Hz), 0.99 (s, 3), 1.11 (s, 3), 1.12 (s, 3), 1.40 (br s, 1, OH), 1.45-1.70 (m, 6), 1.72-1.85 (m, 3), 1.82-2.08 (m, 2), 2.18-2.28 (m, 1), 2.29 (quint, 1, J = 9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, $CDCl_3$ int): δ = 8.31 (q), 14.85 (t), 28.39 (q), 28.48 (q), 30.41 (q), 30.63 (s), 31.45 (t), 35.78 (t), 36.15 (t), 37.84 (d), 42.37 (s), 43.90 (d), 50.06 (d), 51.28 (t), 85.87 (s); MS m/z 222 (1, M^+), 55 (100). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.80; H, 11.81.

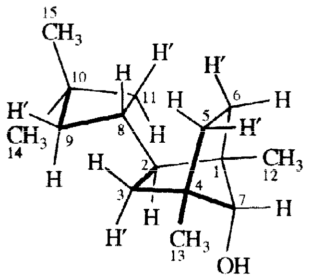
(1*RS*,5*SR*)-3-(3,3-Dimethyl-cyclobutyl)-2,5-dimethyl-bicyclo[3.2.0]hept-2-ene (23): To a stirred solution of **4** (666 mg, 3.00 mmol) in benzene (30 ml) was added a solution of anhydrous p-toluenesulfonic acid in benzene (0.74 M, 4.05 ml, 3.00 mmol) causing an exothermic effect and an instantaneous precipitation of p-toluenesulfonic acid monohydrate. After 1h at 60°C, GC analysis [3 m x 1/4″ all glass system, 15% FFAP on Chromosorb W AW/DMCS, 60/80 mesh, 5 min 100°C, 20°C/min to 180°C, 6 min 180°C; retention times (min): 8.6, 9.1 (**23**), 9.3, 14.1 (**4**)] revealed that the minor components of the initially formed 3.5:4.5:1-mixture of three olefins had been isomerized to the major component **23**. The mixture was washed with water (2 x 30 ml) and dried (Na_2CO_3). The solvent was evaporated (bath temperature 30°C/15 torr) and the residue (750 mg yellow liquid) chromatographed on silica gel (0.05-0.20 mm) in pentane [column 12 x 3 cm; $R_f = 0.72$ (**23**)] to yield 520 mg (85%) of **23** as colourless liquid (purity 92% GC). An analytically pure sample was obtained by preparative GC. ^1H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int): δ = 1.03 (s, 3), 1.18 (s, 3), 1.23 (s, 3), 1.53 (br s, 3), 1.55-1.85 (m, 7), 2.10-2.25 (m, 1), 2.25 (br s, 2), 2.53-2.61 (m, 1), 3.19 (quint, 1, J = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, $CDCl_3$ int): δ = 11.79 (q), 22.97 (t), 25.05 (q), 27.17 (d), 28.17 (q), 30.79 (q), 31.72 (s), 33.24 (t), 39.06 (t), 39.64 (t), 41.34 (s), 47.88 (t), 55.86 (d), 133.36 (s), 137.72 (s); MS m/z 204 (M^+, 4), 176 (31), 120 (82), 105 (84), 91 (100). HRMS m/z (M^+) calc 204.1878, obsd 204.1878.

(1*RS*,2*SR*,4*SR*,7*RS*)-2-(3,3-Dimethyl-cyclobutyl)-1,4-dimethyl-bicyclo[2.2.1]heptan-7-ol (24), (1*RS*,2*RS*,4*SR*,7*RS*)-2-(3,3-Dimethyl-cyclobutyl)-1,4-dimethyl-bicyclo[2.2.1]heptan-7-ol (25) and (1*RS*,2*SR*,6*SR*,8*SR*,11*RS*)-1,4,4,8-Tetramethyl-tricyclo[6.2.1.0^{2,6}]undecan-11-ol (Cerapicol) (8): To a stirred solution of **4** (1.11 g, 5.0 mmol) in pentane (10 ml) was added trifluoroacetic acid (5.0 ml) and the reaction progress of the resulting homogeneous mixture monitored by GC [3 m x 1/4″ all glass system, 15% FFAP on Chromosorb W AW/DMCS, 60/80 mesh, 5 min 100°C, 20°C/min to 180°C, 15 min 180°C; retention times (min): 9.1 (**23**), 9.2, 10.1, 10.8 (trifluoroacetates), 14.1 (**4**)]. After 1 h at room temperature, the starting alcohol **4** and the intermediately formed olefin **23** had been consumed. Water (10 ml) was added, the phases were separated and the aqueous phase was extracted with pentane (10 ml). The combined organic phases were dried (Na_2CO_3) and evaporated to dryness (bath temperature 30°C/15 torr) to yield 1.52 g (96%) of a mixture of trifluoroacetates als yellowish oil. This material was dissolved in ether (10 ml) and added to a suspension of $LiAlH_4$ (570 mg, 15.0 mmol) in ether (30 ml) causing a slightly exothermic effect. After 30 min at room temperature GC analysis [3 m x 1/4″ all glass system, 15% FFAP on Chromosorb W AW/DMCS, 60/80 mesh, 5 min 100°C, 20°C/min to 180°C, 15 min 180°C; retention times (min): 9.1, 18.6 (**25**), 19.2 (**24**), 22.6 (**8**)] indicated that the reduction was complete. The mixture was hydrolyzed by successive addition of water (0.6 ml), 15% NaOH (0.6 ml) and water (1.8 ml), the liquid phase was decanted, the residue was extracted with ether (10 ml) and the combined organic phases were concentrated (bath temperature 35°C/15 torr) to yield 1.18 g (106%) of an oily residue, containing 41% **24**, 25% **25** and 12% **8** according to GC. Separation was achieved by a combination of column chromatography and GC. First, the whole material was chromatographed on silica gel (0.05-0.20 mm) in dichloromethane (column 90 x 3 cm) yielding fractions A (480 mg, R_f = 0.68-0.52), B (120 mg, R_f = 0.52- 0.43), C (80 mg, R_f = 0.43-0.39), D (400 mg, R_f = 0.39-0.36) and E (40 mg, R_f = 0.36).

Then, fraction A, containing 70% **25** and 21% **8**, and fraction D, containing 94% **24**, were subjected to preparative GC [3 m x 1/4″ all glass system, 15% FFAP on Chromosorb W AW/DMCS, 60/80 mesh, 200°C, retention times (min): 5.3 (**25**), 5.5 (**24**). 7.5 (**8**)]. **8** and **25** were obtained as colourless liquids and **24** as an amorphous solid, mp 50-60°C. The same rearrangement was brought about by substituting **23** for **4** under otherwise unchanged conditions. The spectroscopic assignments for **8** and **24** refer to the following numbering:



8



24

8: ^{1}H NMR (500 MHz, C_6D_6, C_6D_5H int): δ = 0.863 (s, 3, 13-H), 0.900 (d, 1, J = 4 Hz, OH), 0.982 (s, 3, 15-H), 1.013 (s, 3, 12-H), 1.060 (br dd, 1, J = 13, 7.5 Hz, 7-H), 1.124 (dddd, 1, J = 12, 12, 3.5, 1.5 Hz, 9-H), 1.180 (s, 3, 14-H), 1.190 (ddd, 1, J = 12, 12, 4.5 Hz, 10-H), 1.246 (br dd, 1, J = 13.5, 3.5, 5-H), 1.295 (ddd, 1, J = 12, 10, 3.5, 10-H′), 1.338 (br dd, 1, J = 13, 6.5 Hz, 3-H), 1.446 (ddd, 1, J = 12, 10, 4.5 Hz, 9-H′), 1.612 (br dd, 1, J = 13, 13 Hz, 7-H′), 1.745 (ddd, 1, J = 13.5, 8.5, 1 Hz, 5-H′), 1.784 (ddd, 1, J = 13, 8, 6.5 Hz, 2-H), 2.110 (ddddd, 1, J = 13, 8.5, 8, 7.5, 3.5 Hz, 6-H), 2.322 (br dd, 1, J = 13, 13 Hz, 3-H′), 2.840 (br d, J = 4 Hz, 11-H); ^{13}C NMR (75 MHz, C_6D_6, C_6D_6 int): δ = 24.42 (q, C-12), 25.69 (q, C-13), 30.86 (q, C-15), 31.13 (t, C-9), 32.34 (q, C-14), 35.17 (d, C-6), 36.07 (t, C-9), 38.33 (s, C-4), 38.44 (t, C-7), 41.24 (s, C-1 or C-8), 42.15 (s, C-8 or C-1), 42.98 (t, C-3), 47.94 (t, C-5), 51.00 (d, C-2), 84.17 (d, C-11); MS m/z 222 (M$^+$, 80), 207 (46), 204 (42), 191 (72), 189 (78), 176 (51), 175 (36), 161 (46), 95 (100). HRMS m/z (M$^+$) calc 222.1983, obsd 222.1983.

24: ^{1}H NMR (500 MHz, C_6D_6, C_6D_5H int): δ = 0.780 (ddd, 1, J = 12, 5, 1 Hz, 3-H), 0.968 (s, 3, 12-H or 13-H), 0.972 (s, 3, 13-H or 12-H), 1.027 (s, 3, 14-H), 1.042 (dddd, 1, J = 12, 12, 5, 2 Hz, 6-H), 1.134 (s, 3, 15-H), 1.155 (ddd, 1, J = 12, 10, 5 Hz, 5-H), 1.165 (br s, 1, OH), 1.245 (dddd, 1, J = 12, 12, 5, 3.5 Hz, 5-H′), 1.455 (br dd, 1, J = 10.5, 9.5 Hz, 11-H or 9-H), 1.506 (br dd, 1, J = 10.5, 9.5 Hz, 9-H or 11-H), 1.525 (ddd, 1, J = 12, 10, 5 Hz, 6-H′), 1.752 (dddd, 1, J = 10.5, 8, 4, 1 Hz, 11-H′ or 9-H′), 1.832 (ddd, J = 12, 12, 3.5 Hz, 3-H′), 1.838 (dddd, 1, J = 10.5, 8, 4, 1 Hz, 9-H′ or 11-H′), 1.944 (dddd, 1, J = 12, 10, 5, 2 Hz, 2-H), 2.238 (ddddd, J = 10, 9.5, 9.5, 8, 8 Hz, 8-H), 2.875 (br s, 1, 7-H); ^{13}C NMR (75 MHz, C_6D_6, C_6D_6 int): δ = 18.46 (q, C-12 or C-13), 18.74 (q, C-13 or C-12), 27.55 (t, C-6), 28.58 (q, C-14), 29.85 (d, C-8), 31.30 (q, C-15), 32.45 (s, C-10), 33.82 (t, C-5), 39.85 (t, C-3), 40.96 (t, C-9 or C-11), 41.92 (t, C-11 or C-9), 44.75 (s, C-1), 48.91 (s, C-4), 49.14 (d, C-2), 88.28 (d, C-7); MS m/z 222 (M$^+$, 5), 193 (14), 112 (100). HRMS m/z (M$^+$) calc 222.1983, obsd 222.1983.

25: ^{1}H NMR (500 MHz, C_6D_6, C_6D_5H int): δ = 0.86 (br s, 1, OH), 0.955 (s, 3), 0.960 (s, 3), 1.06 (s, 3), 1.13 (s, 3), 1.13-1.25 (m, 4), 1.29-1.45 (m, 5), 1.87-1.94 (m, 2), 2.58-2.68 (m, 1), 2.80 (br s, 1); ^{13}C NMR (75 MHz, C_6D_6, C_6D_6 int): δ = 16.32 (q), 18.35 (q), 28.82 (q), 31.54 (s), 31.59 (q), 32.68 (d), 33.07 (t), 36.20 (t), 40.56 (t), 40.78 (t), 43.74 (t), 44.85 (s), 48.20 (s), 54.93 (d), 86.80 (d); MS m/z 222 (M$^+$, 2), 193 (8), 112 (100). HRMS m/z (M$^+$) calc 222.1983, obsd 222.1983.

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14 Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647-2650.
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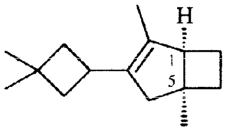
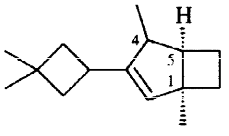
16. All stereoisomers of the following compounds have been taken into account: (1*RS*,5*SR*)-3-(3,3-dimethyl-cyclobutyl)-2,5-dimethyl-bicyclo[3.2.0]-hept-2-ene (**23**), (1*RS*,5*RS*)-3-(3,3-dimethyl-cyclobutyl)-1,4-dimethyl-bicyclo[3.2.0]hept-2-ene (**29**) and (1*SR*,5*RS*)-3-(3,3-dimethyl-cyclobutylidene)-1,4-dimethyl-bicyclo[3.2.0]heptane (**30**). The heats of formation (kcal/mol) were calculated using MMP2 (Sprague, J. T.; Tai, J. C.; Yuh, Y.; Allinger, N. L. *J. Comput. Chem.* **1987**, *8*, 581-603) in connection with the conformational search routine HUNTER (Weiser, J.; Holthausen, M. C.; Fitjer, L. *J. Comput. Chem.* **1997**, *18*, 1265-1281) and are as follows:



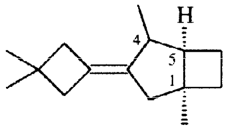
23

5.1



29

7.8 (4*RS*)
6.6 (4*SR*)



30

8.3 (4*RS*)
7.4 (4*SR*)

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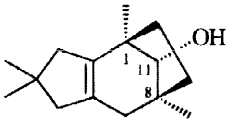
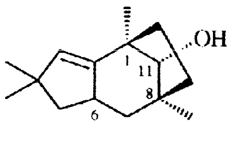
18. All stereoisomers of the following compounds have been taken into account: (1*RS*,8*SR*,11*RS*)-1,4,4,8-tetramethyl-tricyclo[6.2.1.0^{2,6}]undec-2(6)-en-11-ol (**27**), (1*RS*,8*SR*,11*RS*)-1,4,4,8-tetramethyl-tricyclo[6.2.1.0^{2,6}]undec-2-en-11-ol (**31**), (1*RS*,8*SR*,11*RS*)-1,4,4,8-tetramethyl-tricyclo[6.2.1.0^{2,6}]undec-5-en-11-ol (**32**) and (1*RS*,8*RS*,11*RS*)-1,4,4,8-tetramethyl-tricyclo[6.2.1.0^{2,6}]undec-6-en-11-ol (**33**). The heats of formation were calculated as indicated in ref.[16] and are as follows:



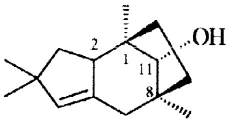
27

-77.0



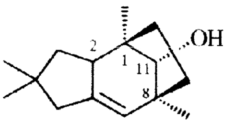
31

-71.6 (6*SR*)
-67.6 (6*RS*)



32

-67.2 (2*SR*)
-71.6 (2*RS*)



33

-69.9 (2*SR*)
-69.9 (2*RS*)

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