An enantiospecific approach to pinguisanes from (*R*)-carvone. Total synthesis of (+)-pinguisenol †

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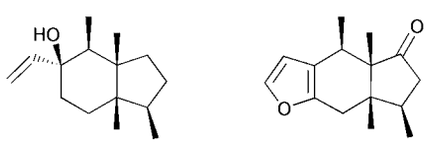
Received (in Cambridge, UK) 14th June, Accepted 4th July 2000
Published on the Web 1st August 2000

Enantiospecific total synthesis of (+)-pinguisenol **1**, a sesquiterpene containing a *cis*-1,2,6,7-tetramethylbicyclo-[4.3.0]nonane carbon framework incorporating two vicinal quaternary carbon atoms and four *cis*-oriented methyl groups on four contiguous carbon atoms, isolated from a liverwort, is described. The orthoester Claisen rearrangement of the allyl alcohol **9**, obtained from (*R*)-carvone, generates the ester **12**. Intramolecular cyclopropanation of the diazo ketone **13**, derived from the ester **12**, furnishes the tricyclic ketone **7**. Degradation of the isopropenyl group followed by regioselective reductive cyclopropane ring cleavage transforms compound **7** into the hydroxy ketone **21**. Wolff–Kishner reduction of the hydroxy ketone **21** followed by oxidation and Grignard reaction furnishes pinguisenol (+)-**1**.

The creativity of Nature in devising varied molecular architecture is revealed through the isolation of a wide range of natural products with remarkable skeletal complexity and multifarious functionalities. Among the natural products, terpenoids (isoprenoids) occupy a special position on account of their widespread occurrence and the bewildering array of carbocyclic skeleta that they embody. Sesquiterpenes, composed of three isoprene units, biogenetically derived from farnesyl pyrophosphate, are assembled in acyclic, monocyclic, bicyclic, tricyclic and even tetracyclic structures containing small, medium and large rings with a wide range of functionalities.[1] Liverworts are endowed with a rich and wide variety of sesquiterpenoids, such as acorane, aristolane, azulene, cedrane, chamigrane, caryophyllane, himachalane, longifolane, thapsane, pinguisanes, *etc*.[2] An important endogenous character of the Hepaticae family is that most of the sesquiterpenoids from liverworts are enantiomeric to those found in higher plants. In 1976 Asakawa and co-workers,[3a] have reported the isolation of the sesquiterpene pinguisenol **1** from the liverwort *Porella vernicosa*. Pinguisenol **1** belongs to the pinguisane group of sesquiterpenes, whose first member pinguisone **2** was isolated in 1969 by Benesova and co-workers from the essential oil obtained from the pentane extract of liverwort *Aneura pinguis* (L.) Dum.[3b] Asakawa and co-workers on the basis of spectral and chemical studies unambiguously determined the structure of pinguisenol **1**. Recently, the relative stereostructure of pinguisenol **1** was established by the total synthesis of the racemic compound.[4] Since the isolation of pinguisone **2**, more than 25 pinguisanes have been isolated from various liverworts such as the families *Lejeuneaceae*, *Porellaceae*, *Trichocoleaceae*, *Ptilidiaceae* and *Aneuraceae*. A notable structural feature of these sesquiterpenes is that almost all these compounds have a *cis*-fused 1,2,6,7-tetramethylbicyclo-[4.3.0]nonane framework **3** incorporating two vicinal quaternary carbon atoms and four methyl groups attached to four contiguous carbon atoms, in an all-*cis* orientation.[3,5] Biosynthetically these compounds are interesting. Earlier[6] the biosynthesis of these compounds was explained from farnesyl pyrophosphate *via* the formation of, first, bisabolane and then acorane, followed by a series of 1,2-migrations eventually leading to the pinguisane skeleton. Recently, Tazaki and co-workers,[7] on the basis of labelling studies, postulated their plausible biosynthetic pathway *via* trifareinyl cation. Recently, we have accomplished[8] a formal total synthesis of pinguisenol (±)-**1** *via* the Schinzers ketone **4**. Elated by the successful completion of the formal total synthesis of racemic pinguisenol **1**, we embarked on the enantiospecific synthesis of pinguisenol and a few other pinguisanes starting from (*R*)-carvone **5**, and herein we describe the details of the first enantiospecific total synthesis of (+)-pinguisenol (+)-**1**.[9]



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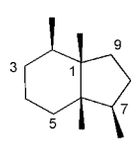

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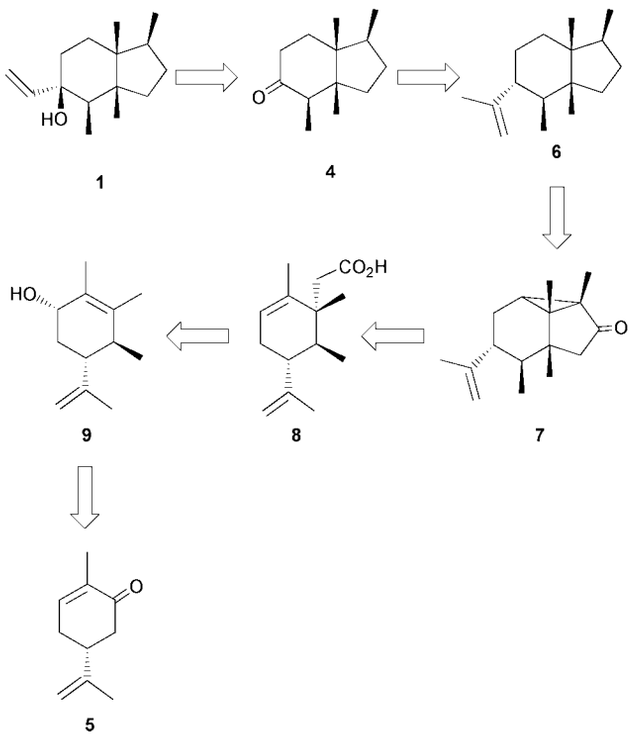
Results and discussion

In the last two decades overwhelming emphasis on the use of carbohydrates[10] as chirons in natural product synthesis has somewhat marginalised the importance of the abundantly available monoterpenes[11] as chiral building blocks in asymmetric synthesis. This has come despite the fact that many monoterpenes are cheap, readily accessible and are endowed with only one or two chiral centres with modest functionality, which means it does not require recourse to wasteful manoeuvres to dispense with excessive chirality or functionality. We have successfully employed the readily available monoterpene (*R*)-carvone **5** as the chiral starting material in the synthesis of a variety of natural products.[12] For the enantiospecific synthesis of pinguisanes, the isopropenyl group in carvone **5** was readily identified as a masked hydroxy group. The retrosynthetic analysis of chiral pinguisenol **1** *via* the Schinzer's ketone[4] **4** based on a combination of a Claisen rearrangement and intramolecular diazo ketone cyclopropanation reactions is depicted

† Chiral synthons from carvone, Part 44. For part 43, see ref. 21.

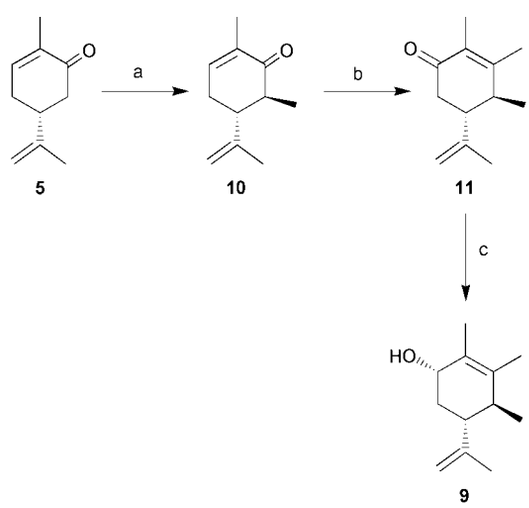
DOI: 10.1039/b004770h



Scheme 1

in Scheme 1. It was conceived that degradation of the isopropenyl side-chain of 10-methylenepinguisane **6** would give the Schinzer's ketone **4**. The 10-methylenepinguisane **6** could, in turn be obtained from the tricyclic ketone **7** *via* regioselective reductive cyclopropane cleavage and deoxygenation of the ketone. An intramolecular diazo ketone cyclopropanation reaction would generate the tricyclic ketone **7** from the γ,δ-unsaturated acid **8**, which in turn could be obtained *via* Claisen rearrangement of the allyl alcohol **9**. The allyl alcohol **9** could be obtained from carvone **5** *via trans*-6-methylcarvone **10**.

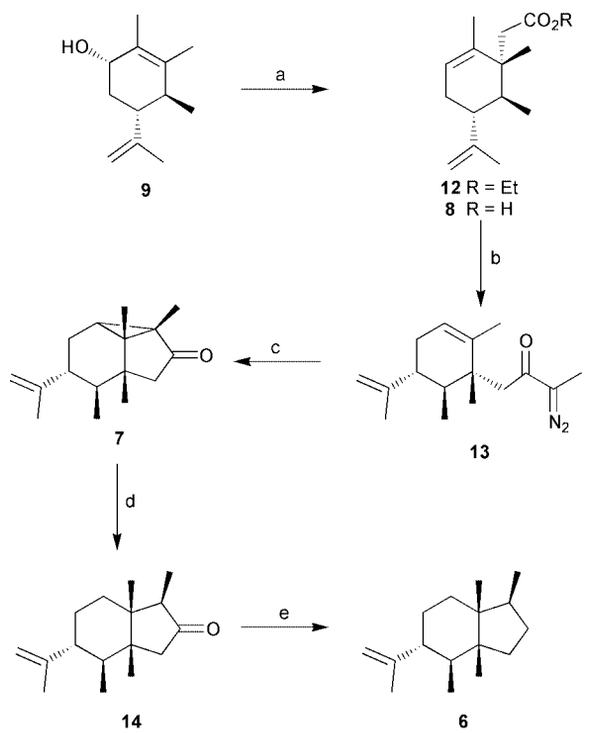
The requisite starting material *trans*-6-methylcarvone **10** was prepared by kinetic alkylation[13] of (*R*)-carvone **5** which is less expensive than (*S*)-carvone. Thus, regioselective alkylation of (*R*)-carvone **5** employing lithium diisopropylamide (LDA) and methyl iodide at −10 °C generated a 3:2 mixture of *trans*- and *cis*-6-methylcarvone **10** in 98% yield (Scheme 2). Treatment



Scheme 2 *Reagents and conditions*: (a) i, LDA, MeI; ii, DBU; iii, recrystallisation; (b) i, MeMgI; ii, PCC–silca gel; (c) $LiAlH_4$.

of this 3:2 epimeric mixture of 6-methylcarvone **10** with one mole equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature furnished a 3:1 mixture of *trans*- and *cis*-6-methylcarvone **10**, which on low-temperature recrystallisation in hexanes yielded stereochemically pure *trans*-6-methylcarvone **10**. Next, attention was turned towards the transformation of *trans*-6-methylcarvone **10** into the allyl alcohol **9**. An alkylative 1,3-enone transposition strategy[14] was chosen for the conversion of *trans*-6-methylcarvone **10** into *trans*-3,4-dimethylcarvone **11**. Consequently, regioselective 1,2-addition of methylmagnesium iodide to *trans*-6-methylcarvone **10**, followed by oxidation of the resulting allylic *tertiary* alcohol with pyridinium chlorochromate (PCC) and silica gel generated *trans*-3,4-dimethylcarvone **11** in 74% yield. Lithium aluminium hydride reduction of the enone **11** in diethyl ether at −70 °C furnished the allyl alcohol **9** in 83% yield, with excellent regio- and stereoselectivity. The *syn* stereochemistry of the hydroxy and isopropenyl groups in the allyl alcohol **9** was assigned based on the preferential axial approach of the hydride as both the C-4 and C-5 substituents direct the incoming hydride *anti* to the C-5 isopropenyl group.[15]

For the creation of the first quaternary centre an orthoester variant of the Claisen rearrangement[16] was employed. Thus, thermal activation of a solution of the allyl alcohol **9**, triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube furnished the diene ester **12** in 65% yield, which on base-catalysed hydrolysis furnished the acid **8** (see Scheme 3).



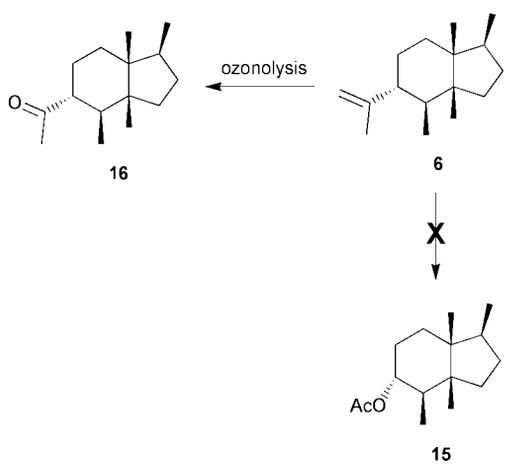
Scheme 3 *Reagents and conditions*: (a) i, $CH_3C(OEt)_3$, $EtCO_2H$, reflux; ii, NaOH; (b) i, $(COCl)_2$; ii, CH_3CHN_2; (c) $CuSO_4$; (d) Li, liq. NH_3; (e) Wolff–Kishner reduction.

The stereochemistry of the newly created quaternary centre rests secured from the well established stereospecificity of the Claisen rearrangement. An intramolecular diazo ketone cyclopropanation reaction[17] was employed for the stereoselective creation of the second quaternary carbon. It was contemplated that cyclopropanation of the diazo ketone **13** followed by regioselective cyclopropane cleavage of the resulting tricyclic ketone will also introduce the requisite fourth methyl group on the fourth contiguous carbon atom in a stereoselective manner. Consequently, treatment of the acid **8** with oxalyl dichloride in benzene followed by reaction of the resulting acid chloride with an excess of ethereal solution of diazoethane furnished the diazo ketone **13**. Anhydrous copper(II)-sulfate-catalysed decomposition of the diazo ketone **13** in refluxing cyclohexane,

using a tungsten lamp, led to the intramolecular insertion of the intermediate keto carbenoid into the ring olefinic moiety in a regio- and stereoselective manner, resulting in the formation of the tricyclic ketone **7** in 52% yield (from the diene acid **8**), whose structure rests secured from its spectral data. The stereoselective formation of the tricyclic ketone **7** was due to the approach of the intermediate carbenoid from the *syn* face of the olefin.

After successful synthesis of the tricyclic ketone **7**, which incorporates the *cis* fused-six–five bicyclic system with four methyl groups on four contiguous carbon atoms in an all-*cis* fashion, the stage was set for further elaboration into pinguisanes. Accordingly, reductive cyclopropane ring cleavage, deoxygenation of carbonyl moiety and degradation of the isopropenyl group were addressed, sequentially. For the reductive cleavage of the cylopropane bond, standard Birch reduction conditions were employed since it is well established that the cyclopropane bond[18] which has better overlap with the π-orbital of the carbonyl bond will be cleaved under these conditions. Thus, treatment of the tricyclic ketone **7** with lithium in liquid ammonia furnished the bicyclic ketone **14** regioselectively in 81% yield. It is worth noting that the bicyclic ketone **14** contains all the carbons of pinguisanes with the appropriate stereochemistry *i.e.*, the bicyclic ketone **14** is 10-methylene-pinguisan-8-one or 10-methylpinguis-10-en-8-one. Huang-Minlon-modified Wolff–Kishner reduction of the bicyclic ketone **14** with hydrazine hydrate in diethylene glycol and ethylene glycol furnished 10-methylenepinguisane **6** (or 10-methylpinguis-10-ene) in 70% yield.

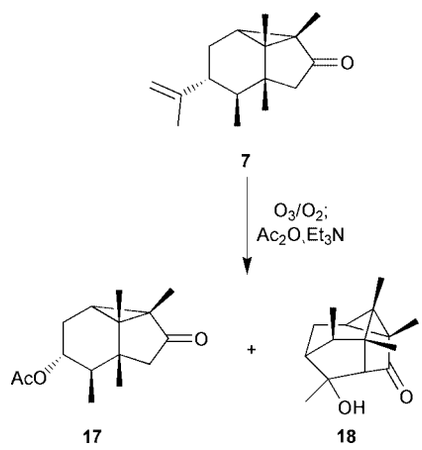
Next, our attention was turned towards degradation of the isopropenyl side-chain for conversion of 10-methylene-pinguisane **6** in to the Schinzer's ketone **4**. It was anticipated that the isopropenyl group could be converted into an acetoxy group by employing a one-pot ozonation–Criegee rearrangement sequence.[19] Accordingly, ozonation, in methanol–methylene dichloride, of the isopropenyl moiety in 10-methylene-pinguisane **6**, followed by treatment of the intermediate methoxy hydroperoxide with pyridine or triethylamine and *p*-nitrobenzoyl chloride in refluxing benzene, however, failed to give the Criegee rearrangement product **15**, and instead the simple ozonolysis product pinguisan-10-one **16** was obtained (Scheme 4). Quite expectedly, ozonolysis of 10-methylene-



Scheme 4

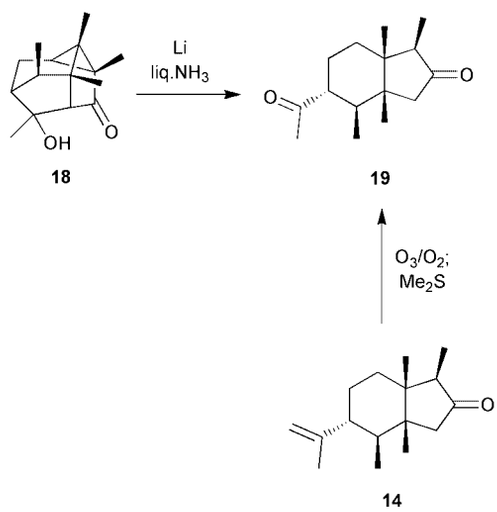
pinguisane **6** in methanol–methylene dichloride followed by reductive work-up with dimethyl sulfide also furnished pinguisan-10-one **16**, whose structure was established on the basis of its spectral data. Since the one-pot Criegee rearrangement strategy was unsuccessful for the generation of the acetate **15**, a stepwise sequence was attempted *via* Baeyer–Villiger oxidation of **16**. However, treatment of pinguisan-10-one **16** with *m*-chloroperbenzoic acid (MCPBA) under a variety of conditions failed to generate the acetate **15**. In another direction for the generation of Schinzer's ketone **4**, brief (and unsuccessful) attempts were made to isomerise the isopropenyl group to an isopropylidene group in 10-methylenepinguisane **6** and to generate the thermodynamic enol acetate of the ketone **16**.

The unexpected failure of the attempted Baeyer–Villiger oxidation of pinguisan-10-one **16** forced us to modify our synthetic sequence, and degradation of the isopropenyl moiety was carried out at an earlier stage of the sequence. Thus, ozonation of the tricyclic ketone **7** in methanol–methylene dichloride followed by treatment of the resulting methoxy hydroperoxide with acetic anhydride and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in refluxing benzene, furnished a 2:3 mixture of the rearrangement product **17** and the tetracyclic keto alcohol **18** (Scheme 5), which were separated by employing silica gel



Scheme 5

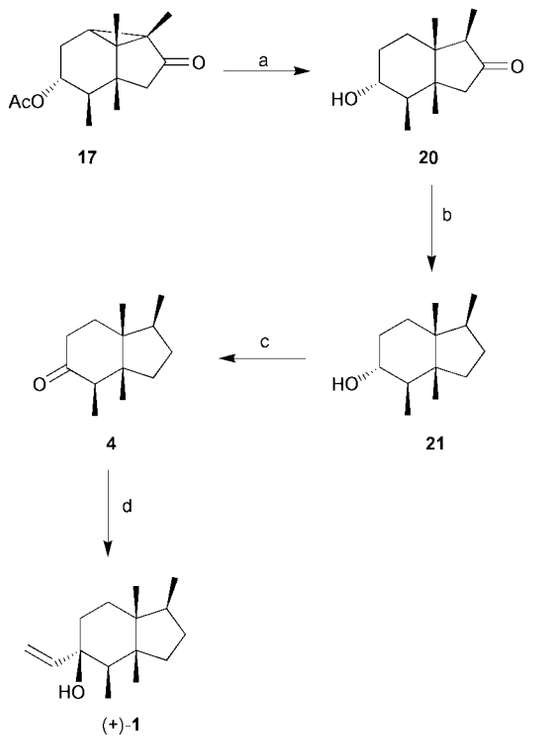
column chromatography. Formation of the keto alcohol **18** can be explained *via* the base-catalysed intramolecular aldol condensation of the normal ozonolysis product as the two carbonyl functions are spatially close to each other due to its convex topology. The structure of keto alcohol **18** was confirmed by chemical transformation. Treatment of keto alcohol **18** with lithium in liquid ammonia furnished pinguisane-8,10-dione **19** in 70% yield (Scheme 6). Ozonolysis of the bicyclic



Scheme 6

ketone **14** in methanol–methylene dichloride followed by reductive work-up with dimethyl sulfide furnished the dione **19** in 69% yield, confirming the structure of the keto alcohol **18**.

Next, our attention was turned towards the conversion of the tricyclic acetoxy ketone **17** into Schinzer's ketone **4**. Treatment of the acetoxy ketone **17** with lithium in liquid ammonia furnished the keto alcohol **20** in 85% yield, *via* regioselective cleavage of the cyclopropane ring and hydrolysis of the acetoxy group (Scheme 7). Modified Wolff–Kishner reduction of the



Scheme 7 *Reagents and conditions*: (a) Li, liq. NH_3; (b) Wolff–Kishner reduction; (c) PCC, silica gel; (d) CH_2=CHMgBr.

keto alcohol **20** furnished the alcohol **21** in 69% yield, which on oxidation with PCC and silica gel furnished the bicyclic ketone (−)-**4**, which was identified by comparison of the TLC and spectral data with those of the racemic Schinzer's ketone **4**.[4,8] Finally, addition of vinylmagnesium bromide at −10 °C to the bicyclic ketone (−)-**4** furnished pinguisenol (+)-**1** in 80% yield. The spectral data (IR, ^{1}H and ^{13}C NMR) of the pinguisenol obtained in this study were found to be identical with those of the racemic sample reported by Schinzer and Ringe.[4] The synthetic (+)-pinguisenol (+)-**1** was found to be the optical antipode of the natural product,[3a] thus establishing the absolute configuration of the natural pinguisenol (−)-**1** as *1S*,*2S*,*3S*,*6S*,*7R*.

In conclusion, we have developed an enantiospecific approach to pinguisanes starting from (*R*)-carvone by employing a Claisen rearrangement, an intramolecular diazo ketone cyclopropanation and a regioselective reductive cyclopropane ring-cleavage sesquence. Synthesis of (+)-pinguisenol was accomplished in thirteen steps starting from *trans*-6-methylcarvone in an overall yield of 2.5%, which established the absolute stereochemistry of the natural pinguisenol.

Experimental[20]

Ozonolysis experiments were carried out using a Fischer 502 ozone generator. In the liquid ammonia reactions, the coolant used in the Dewar condenser is a combination of ethanol and liquid nitrogen. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are given in the units of 10^{-1} deg cm^2 g^{-1}.

(5*R*,6*S*)-(+)-5-Isopropenyl-2,6-dimethylcyclohex-2-enone 10[13]

To a cold (−10 °C), magnetically stirred solution of diisopropylamine (17.6 ml, 124.8 mmol) in anhydrous tetrahydrofuran (THF) (90 ml) was slowly added a hexane solution of *n*-BuLi (1.6 M; 76 ml, 124.8 mmol) over a period of 20 min. To the LDA thus formed was added dropwise a solution of (*R*)-carvone **5** (14.4 g, 95.7 mmol) in anhydrous THF (135 ml) and the mixture was stirred for 2 h at the same temperature. The enolate was then treated with an excess of methyl iodide (30 ml, 482 mmol) and the reaction mixture was stirred at room temperature for 12 h. It was then diluted with water and extracted with diethyl ether (3 × 30 ml). The combined organic extract was washed successively with 3 M aq. HCl, saturated aq. $NaHCO_3$, and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column, using ethyl acetate–hexane (1:40 to 1:20) as eluent, furnished a 3:2 epimeric mixture of 6-methylcarvone **10** (15.4 g, 98%) as an oil.

To a magnetically stirred solution of a 3:2 epimeric mixture of 6-methylcarvone **10** (1 g, 6.09 mmol) in CH_2Cl_2 (10 ml) was added DBU (0.9 ml, 6.09 mmol) and the reaction mixture was stirred at room temperature for 24 h. It was then washed successively with 1 M aq. HCl, water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column, using ethyl acetate–hexane (1:40) as eluent furnished a 3:1 epimeric mixture of 6-methylcarvone **10** (950 mg, 95%). Repeated recrystallisation of the epimeric mixture at −10 °C using hexanes as solvent furnished stereochemically pure *trans*-6-methylcarvone **10** (450 mg, 45%), mp 38–40 °C (lit.,[13] 36–38 °C); $[a]_D^{23}$ +2.03 (*c* 4.3, $CHCl_3$); ν_{max} (neat) 1670, 890, 850 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 6.70 (1 H, m, H-3), 4.80 (2 H, s, C=CH_2), 2.20–2.50 (4 H, m), 1.76 (3 H, s) and 1.69 (3 H, s) (together 2 × olefinic CH_3), 1.05 (3 H, d, *J* 6.5 Hz, *sec*-CH_3); δ_C (22.5 MHz; $CDCl_3$) 200.8 (s), 145.3 (s), 142.8 (d), 134.3 (s), 112.7 (t), 50.3 (d), 43.8 (d), 30.9 (t), 17.8 (q), 15.7 (q), 12.2 (q); HRMS *m*/*z* for $C_{11}H_{16}O$ (Calc.: *M,* 164.1202. Found: M^+, 164.1197).

(4*S*,5*R*)-(−)-5-Isopropenyl-2,3,4-trimethylcyclohex-2-enone 11

To a cold (−5 °C), magnetically stirred solution of methylmagnesium iodide (12.5 mmol) [prepared from magnesium (300 mg, 12.5 mmol) and methyl iodide (2.27 g, 16 mmol) and a catalytic amount of iodine] in 30 ml of dry diethyl ether was added a solution of *trans*-6-methylcarvone **10** (650 mg, 3.96 mmol) in dry diethyl ether over a period of 30 min. The reaction mixture was slowly warmed to room temperature and stirred for 3 h. It was then poured into saturated aq. NH_4Cl and extracted with diethyl ether (2 × 15 ml). The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished a tertiary alcohol.

To a magnetically stirred suspension of PCC (1.5 g, 7.0 mmol) and silica gel (1.5 g) in anhydrous CH_2Cl_2 (5 ml) was added a solution of the tertiary alcohol obtained above in dry CH_2Cl_2 (2 ml) in one portion. The reaction mixture was stirred at room temperature for 3 h, filtered through a silica gel column, and the column was eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica gel column, using ethyl acetate–hexane (1:40 to 1:10) as eluent, furnished the enone **11** (522 mg, 74% yield) as an oil, $[a]_D^{24}$ −7.7 (*c* 6.0, $CHCl_3$); ν_{max} (neat) 1660, 890 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 4.83 (1 H, s) and 4.73 (1 H, s) (together C=CH_2), 2.30–2.60 (4 H, m), 1.93 (3 H, s, 3-CH_3), 1.77 (3 H, s), 1.7 (3 H, s, 2-CH_3), 1.19 (3 H, d, *J* 7.5 Hz, *sec*-CH_3); δ_C (100 MHz; $CDCl_3$) 198.3, 157.3, 146.1, 130.5, 112.5, 48.4, 40.4, 40.0, 20.1, 16.7, 17.9, 11.2; HRMS *m*/*z* for $C_{12}H_{18}O$ (Calc.: *M,* 178.1358. Found: M^+, 178.1346).

(1*S*,4*S*,5*R*)-(−)-5-Isopropenyl-2,3,4-trimethylcyclohex-2-enol 9

To a magnetically stirred, cold (−78 °C) solution of the enone **11** (520 mg, 2.93 mmol) in diethyl ether (16 ml) was added $LiAlH_4$ (80 mg, 2.1 mmol). The reaction mixture was stirred at −70 °C for 2 h, and then allowed to attain room temperature

over a period of 30 min. The reaction was quenched first with wet diethyl ether and then with dil. aq. HCl. It was then extracted with ether (3 × 10 ml) and the combined ether extract was washed successively with saturated aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate–hexane (1 : 10 to 1 : 5) as eluent furnished the alcohol **9** (437 mg, 83%) as an oil, $[a]_D^{26}$ −13.0 (*c* 3.2, $CHCl_3$); ν_{max} (neat) 3330, 1635, 885 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 4.79 (1 H, s) and 4.74 (1 H, s) (together C=C*H*$_2$), 4.03 (1 H, m, C*H*OH), 1.50–2.30 (5 H, m), 1.73 (6 H, s) and 1.67 (3 H, s) (together 3 × olefinic CH_3), 0.95 (3 H, d, *J* 7.0 Hz, *sec*-CH_3); δ_C (100 MHz; $CDCl_3$) 149.2, 133.1, 128.6, 111.2, 71.1, 47.3, 38.1, 36.0, 20.2, 18.2, 17.4, 15.3; HRMS *m*/*z* for $C_{12}H_{20}O$ (Calc.: *M,* 180.1514. Found: M^+, 180.1521).

(3*R*,2*S*,5*R*)-(+)-5-Isopropenyl-2,3,4-trimethylcyclohexene-3-acetic acid 8

A solution of the allyl alcohol **9** (2 g, 11.17 mmol), triethyl orthoacetate (10.2 ml, 55.87 mmol) and a catalytic amount (≈5 µl) of propionic acid was placed in two sealed tubes and heated to 175 °C for 5 days in an oil-bath. The reaction mixture was cooled, diluted with diethyl ether (2 × 25 ml), washed successively with 0.5 M aq. HCl, saturated aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column, using ethyl acetate–hexane (1 : 40) as eluent, furnished the ester **12** (1.8 g, 65%) as an oil.

To a magnetically stirred solution of the ester **12** (1.5 g, 6.02 mmol) in methanol (12 ml) was added 10% aq. NaOH (12 ml) and the reaction mixture was refluxed for 6 h. The solvent was evaporated under reduced pressure, the residue was taken in water (25 ml) and washed with CH_2Cl_2 (2 × 15 ml). The aq. phase was acidified with 3 M aq. HCl and extracted with CH_2Cl_2 (2 × 15 ml). The organic extract was then washed successively with water (15 ml) and brine, and dried (Na_2SO_4). Evaporation of the solvent furnished the acid **8** (1.2 g, 90%), which was recrystallised from a mixture of CH_2Cl_2–hexane, mp 62–65 °C; $[a]_D^{24}$ +10.2 (*c* 3.4, $CHCl_3$); ν_{max} (neat) 2900, 1695, 1635, 885 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 5.35–5.55 (1 H, m, H-1), 4.69 (2 H, s, C=C*H*$_2$), 2.52 (2 H, close ABq, *J* 15 Hz, CH_2C=O), 1.70–2.50 (4 H, m), 1.73 (3 H, s) and 1.65 (3 H, s) (together 2 × olefinic CH_3), 0.96 (3 H, s, *tert*-CH_3), 0.83 (3 H, d, *J* 6.4 Hz, *sec*-CH_3); δ_C (22.5 MHz; $CDCl_3$) 178.3 (s), 148.0 (s), 137.7 (s), 123.1 (d), 112.0 (t), 44.8 (d), 41.3 (2 C, s and t), 36.1 (d), 30.9 (t), 21.3 (q), 19.5 (q), 17.9 (q), 13.1(q); HRMS *m*/*z* for $C_{14}H_{22}O_2$ (Calc.: *M,* 222.1619. Found: M^+, 222.1621).

(1*S*,2*S*,4*R*,5*S*,6*R*,9*S*)-(+)-4-Isopropenyl-1,5,6,9-tetramethyltricyclo[4.3.0.0^{2,9}]nonan-8-one 7

A solution of the acid **8** (870 mg, 3.9 mmol) and oxalyl dichloride (1.2 ml, 13.8 mmol) in dry benzene (5 ml) was magnetically stirred for 2 h at room temperature. Evaporation of the excess of oxalyl dichloride and benzene under reduced pressure afforded the corresponding acid chloride, which was taken up in dry diethyl ether (4 ml) and added dropwise to a cold, magnetically stirred ethereal solution of diazoethane (excess, prepared from 5 g of *N*-ethyl-*N*-nitrosourea, 50 ml of 60% aq. KOH and 50 ml of diethyl ether). The reaction mixture was stirred for 2 h at room temperature and the excess of diazoethane and ether were carefully evaporated on a water-bath. Rapid purification of the product by filtration through a silica gel column, using ethyl acetate–hexane (1 : 10) as eluent, furnished the diazo ketone **13** as a yellow oil, ν_{max} (neat) 2220, 1640, 1620, 890 cm^{-1}.

To a magnetically stirred, refluxing (using two 100W tungsten lamps placed near the reaction flask) suspension of anhydrous copper(II) sulfate (870 mg, 5.45 mmol) in dry cyclohexane (60 ml) was added, dropwise, a solution of the diazo ketone **13** in cyclohexane (10 ml) over a period of 30 min and the reaction mixture was refluxed for 4 h. It was then cooled and copper(II) sulfate was filtered off. Evaporation of the solvent and purification of the residue on a silica gel column, using ethyl acetate–hexane (1 : 20) as eluent, furnished the tricyclic ketone **7** (470 mg, 52% from the acid **8**) as a pale yellow oil, $[a]_D^{24}$ +28.0 (*c* 3.8, $CHCl_3$); ν_{max} (neat) 1710, 1640, 1620, 890 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 4.75 (2 H, s, C=C*H*$_2$), 2.15 (1 H, d, *J* 20 Hz) and 1.98 (1 H, d, *J* 20 Hz) (together C*H*$_2$C=O), 1.15–2.00 (5 H, m), 1.65 (3 H, t, *J* 1.1 Hz, olefinic CH_3), 1.24 (3 H, s), 1.20 (3 H, s) and 1.16 (3 H, s) (together 3 × *tert*-CH_3), 0.99 (3 H, d, *J* 6.9 Hz, *sec*-CH_3); δ_C (22.5 MHz; $CDCl_3$) 214.7 (s), 147.7 (s), 111.4 (t), 56.0 (t), 52.0 (d), 43.7 (s), 39.0 (d), 38.3 (s), 37.2 (s), 35.0 (d), 26.0 (q), 24.4 (t), 19.4 (q), 18.6 (q), 16.2 (q), 11.8 (q); HRMS *m*/*z* for $C_{16}H_{24}O$ (Calc.: *M,* 232.1827. Found: M^+, 232.1828).

(1*R*,2*S*,3*R*,6*R*,7*R*)-(−)-3-Isopropenyl-1,2,6,7-tetramethylbicyclo[4.3.0]nonan-8-one (10-methylenepinguisan-8-one) 14

To magnetically stirred, freshly distilled (over sodium) liquid ammonia (50 ml) in a three-necked flask equipped with a Dewar condenser was added a solution of the tricyclic ketone **7** (100 mg, 0.43 mmol) in dry THF (3 ml) followed by freshly cut lithium (15 mg, 2.15 mmol) in small pieces. The resulting blue coloured solution was stirred for 30 min and then the reaction was quenched with solid NH_4Cl. After evaporation of ammonia, the residue was taken in water (10 ml) and extracted with diethyl ether (2 × 10 ml). The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column, using ethyl acetate–hexane (1 : 20) as eluent, furnished the bicyclic ketone **14** (82 mg, 81%) as a colourless oil, $[a]_D^{27}$ −20 (*c* 1.2, $CHCl_3$); ν_{max} (neat) 1740, 1640, 880 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 4.7 (2 H, br s, C=C*H*$_2$), 2.78 (1 H, q, *J* 6.9 Hz), 2.35 (1 H, d, *J* 19.2 Hz) and 2.00 (1 H, d, *J* 19.2 Hz) (together H_2-9), 1.62 (3 H, t, *J* 1.0 Hz, olefinic CH_3), 1.40–1.70 (6 H, m), 0.98 (3 H, s, *tert*-CH_3), 0.92 (3 H, d, *J* 7.0 Hz, *sec*-CH_3), 0.76 (3 H, s, *tert*-CH_3), 0.72 (3 H, d, *J* 6.6 Hz, *sec*-CH_3); δ_C (100 MHz; $CDCl_3$,) 220.9, 148.6, 111.2, 49.0, 48.7, 47.3, 44.2, 42.6, 36.7, 30.3, 27.4, 20.4, 18.4, 14.9, 14.7, 7.9; HRMS *m*/*z* for $C_{16}H_{26}O$ (Calc.: *M,* 234.1984. Found: M^+, 234.1991).

(1*R*,2*S*,3*R*,6*R*,7*S*)-(+)-3-Isopropenyl-1,2,6,7-tetramethylbicyclo[4.3.0]nonane (10-methylenepinguisane) 6

A solution of the bicyclic ketone **14** (73.5 mg, 0.314 mmol) and hydrazine hydrate (0.2 ml, 4.2 mmol) in a mixture of diethylene glycol (2 ml) and ethylene glycol (0.5 ml) was placed in a sealed tube and heated to 180 °C for 2 h. The sealed tube was cooled to 70 °C and treated with a solution of sodium (82 mg, 3.6 mmol) in diethylene glycol (3 ml). The reaction mixture was further heated to 180 °C for 4 h. It was then cooled to room temperature, poured into ice-cold water (5 ml) and extracted with hexane (2 × 10 ml). The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column, using hexane as eluent, furnished 10-methylenepinguisane **6** (48 mg, 70%) as an oil, $[a]_D^{28}$ +30.7 (*c* 2.05, $CHCl_3$); ν_{max} (neat) 1640, 890 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 4.66 (1 H, s) and 4.64 (1 H, s) (together C=CH_2), 2.40 (1 H, q, *J* 6.9 Hz), 1.75–1.90 (5 H, m), 1.62 (3 H, s, olefinic CH_3), 0.70–0.95 (5 H, m), 0.81 (3 H, d, *J* 6.6 Hz, *sec*-CH_3), 0.78 (3 H, s, *tert*-CH_3), 0.67 (3 H, d, *J* 6.6 Hz, *sec*-CH_3), 0.62 (3 H, s, *tert*-CH_3); δ_C (75 MHz; $CDCl_3$) 149.9, 110.3, 49.3, 47.3, 45.2, 35.8, 35.0, 34.4, 30.5, 29.1, 27.2, 19.4, 18.3, 15.1, 14.7, 14.6; *m*/*z*, 220 (M^+, 5%), 207 (15), 137 (99), 123 (55), 109 (100), 95 (88).

(1*R*,2*S*,3*R*,6*R*,7*S*)-(+)-3-Acetyl-1,2,6,7-tetramethylbicyclo-[4.3.0]nonane (pinguisan-10-one) 16

Dry ozone in oxygen gas was passed through a cold (−70 °C) suspension of the alkene **6** (50 mg, 0.227 mmol) and $NaHCO_3$ (5 mg) in 1 : 50 methanol–CH_2Cl_2 (5 ml) until the reaction mixture turned blue in colour. Excess of ozone was flushed off with oxygen. Dimethyl sulfide (0.008 ml, 1.135 mmol)

was added to the reaction mixture at −70 °C, which was then allowed to attain room temperature and was magnetically stirred for 4 h. Evaporation of the solvent and purification of the residue on a silica gel column, using ethyl acetate–hexane (1:20), furnished pinguisan-10-one **16** (34 mg, 68%) as an oil, $[\alpha]_D^{29}$ +14.0 (*c* 3.3, $CHCl_3$); ν_{max} (neat) 1705 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 2.50–2.20 (1 H, m), 2.13 (3 H, s), 2.1–1.2 (10 H, m), 0.87 (3 H, d, *J* 6.3 Hz, *sec*-CH_3), 0.83 (3 H, s), 0.71 (3 H, d, *J* 5.5 Hz, *sec*-CH_3), 0.68 (3 H, s, *tert*-CH_3); δ_C (75 MHz; $CDCl_3$) 213.8, 55.0, 46.9, 45.0, 35.5, 34.9, 33.7, 29.7, 29.3, 28.9, 24.6, 19.2, 15.0, 14.6, 14.4; HRMS *m*/*z* for $C_{15}H_{26}O$ (Calc.: *M,* 222.1984. Found: M^+, 222.1970).

(1*S*,2*S*,4*R*,5*R*,6*R*,9*S*)-(+)-4-Acetoxy-1,5,6,9-tetramethyltricyclo[4.3.0.0^{2,9}]nonane-8-one 17 and (+)-5-hydroxy-2,5,7,8,9-pentamethyltetracyclo[4.3.1.0^{2,9}.0^{4,8}]decan-3-one 18

Pre-cooled, dry ozone in oxygen gas was passed through a cold (−70 °C) suspension of the tricyclic ketone **7** (60 mg, 0.26 mmol) and $NaHCO_3$ (5 mg) in 1:100 methanol–CH_2Cl_2 (1 ml) until the reaction mixture turned blue in colour. Excess of ozone was flushed off with oxygen. The solvent was evaporated *in vacuo* and the residue was dissolved in dry benzene (5 ml). To this mixture were added triethylamine (0.3 ml, 2.16 mmol), acetic anhydride (0.4 ml, 4.2 mmol) and a catalytic amount of DMAP and the mixture was stirred at room temperature for 1 h. Then the reaction mixture was refluxed for 6 h. Upon work-up followed by purification of the residue over a silica gel column, using ethyl acetate–hexane (1:40) as eluent, the keto acetate **17** (20 mg, 31%) was obtained as colourless oil, $[\alpha]_D^{24}$ +3.8 (*c* 1.3, $CHCl_3$); ν_{max} (neat) 1735, 1715 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.72 (1 H, ddd, *J* 12.0, 7.2 and 4.9 Hz, H-4), 2.43 (1 H, ddd, *J* 15.6, 8.9 and 7.4 Hz), 2.26 and 2.17 (2 H, ABq, *J* 19.6 Hz, H_2-7), 2.03 (3 H, s, $OCOCH_3$), 1.60–1.70 (1 H, m), 1.25–1.35 (1 H, m), 1.24 (3 H, s), 1.22 (3 H, s), 1.17 (3 H, s) (together 3 × *tert*-CH_3), 1.15–1.20 (1 H, m), 1.09 (3 H, d, *J* 7.3 Hz, *sec*-CH_3); δ_C (75 MHz; $CDCl_3$) 214.8, 170.7, 75.9, 55.5, 44.1, 41.8, 38.5, 37.1, 32.3, 25.5, 23.8, 21.4, 17.0, 16.2, 12.4; HRMS *m*/*z* for $C_{15}H_{22}O_3$ (Calc.: *M,* 250.1569. Found: M^+, 250.1555).

Further elution of the column with ethyl acetate–hexane (1:10) as eluent furnished the by-product, keto alcohol **18** (28 mg, 46%) as an oil, $[\alpha]_D^{26}$ +7.2 (*c* 3.2, $CHCl_3$); ν_{max} (neat) 3400–3500, 1700 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.42 (1 H, d, *J* 15.0 Hz), 1.94 (1 H, t of d, *J* 15.0 and 6.2 Hz), 1.90 (1 H, s), 1.88 (1 H, s), 1.74 (1 H, d of q, *J* 6.9 and 4.1 Hz), 1.70–1.60 (2 H, m), 1.32 (3 H, s, $HOCCH_3$), 1.19 (3 H, s, *tert*-CH_3), 1.14 (3 H, d, *J* 6.8 Hz, *sec*-CH_3), 1.14 (2 H, s), 1.10 (3 H, s, *tert*-CH_3), 1.04 (1 H, d, *J* 6.2 Hz); δ_C (75 MHz; $CDCl_3$) 215.8, 73.5, 68.9, 49.2, 46.3, 41.6, 40.8, 40.5, 32.0, 30.5, 22.0, 17.6, 15.9, 12.2, 10.8; HRMS *m*/*z* for $C_{15}H_{22}O_2$ (Calc.: *M,* 234.1620. Found: M^+, 234.1621).

(1*R*,2*S*,3*R*,6*R*,7*R*)-(−)-3-Acetyl-1,2,6,7-tetramethylbicyclo-[4.3.0]nonan-8-one (pinguisane-8,10-dione) 19

To magnetically stirred, freshly distilled (over sodium) ammonia (50 ml) in a three-necked flask equipped with a Dewar condenser was added a solution of the keto alcohol **18** (70 mg, 0.3 mmol) in dry THF (3 ml) followed by freshly cut lithium (15 mg, 2.14 mmol) in small pieces. The resulting blue coloured solution was stirred for 30 min and the reaction was quenched with solid NH_4Cl. After evaporation of ammonia, the residue was taken up in water (10 ml) and extracted with diethyl ether (2 × 10 ml). The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column, using ethyl acetate–hexane (1:10) as eluent furnished the dione **19** (49 mg, 70%) as a colourless oil, $[\alpha]_D^{29}$ −8.8 (*c* 2.0, $CHCl_3$); ν_{max} (neat) 1730, 1705 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 2.80 (1 H, q, *J* 6.9 Hz, H-7), 2.43 (1 H, m, H-3), 2.33 (1 H, d, *J* 19 Hz), 2.16 (3 H, s, $CH_3C{=}O$), 1.98 (1 H, d, *J* 19.5 Hz, H^b-9), 1.86 (1 H, q of d, *J* 12 and 6.6 Hz, H-2), 1.75–1.40 (4 H, m), 0.98 (3 H, s, *tert*-CH_3), 0.92 (3 H, d, *J* 6.9 Hz, *sec*-CH_3), 0.80 (3 H, d, *J* 6.6 Hz, *sec*-CH_3), 0.76 (3 H, s, *tert*-CH_3); δ_C (22.5 MHz; $CDCl_3$) 219.1 (s), 212.2 (s), 53.8 (d), 48.0 (t), 47.1 (d), 43.8 (s), 42.0 (s), 36.0 (d), 29.6 (t), 29.3 (q), 24.8 (t), 20.0 (q), 14.5 (2 C, q), 7.7 (q); *m*/*z* 236 (M^+, 16%), 221 (M − Me, 100), 205 (26), 177 (38), 137 (35), 135 (40), 134 (50), 124 (55), 123 (40), 121 (78), 109 (56), 95 (37).

(1*R*,2*R*,3*R*,6*R*,7*R*)-(−)-3-Hydroxy-1,2,6,7-tetramethylbicyclo-[4.3.0]nonan-8-one 20

To magnetically stirred, freshly distilled (over sodium) liquid ammonia (50 ml) in a three-necked flask equipped with a Dewar condenser, was added a solution of the keto acetate **17** (70 mg, 0.28 mmol) in dry THF (3 ml) followed by freshly cut lithium (15 mg, 2.14 mmol) in small pieces. The resulting blue coloured solution was stirred for 20 min and the reaction was quenched with solid NH_4Cl. After evaporation of ammonia, the residue was taken up in water (10 ml) and extracted with diethyl ether (2 × 10 ml). The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the product on a silica gel column, using ethyl acetate–hexane (1:10) as eluent, furnished the keto alcohol **20** (50 mg, 85%) as a colourless oil, $[\alpha]_D^{24}$ −26.3 (*c* 1.8, $CHCl_3$); ν_{max} (neat) 3420, 1730 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.45 (1 H, d of t, *J* 11.3 and 4.4 Hz, C*H*OH), 2.76 (1 H, q, *J* 6.9 Hz, H-7), 2.35 (1 H, d, *J* 19.2 Hz) and 1.96 (1 H, d, *J* 19.2 Hz) (together H_2-9). 1.80–1.90 (1 H, m), 1.40–1.65 (5 H, m), 1.0 (3 H, d, *J* 6.5 Hz, *sec*-CH_3), 0.97 (3 H, s, *tert*-CH_3), 0.92 (3 H, d, *J* 6.9 Hz, *sec*-CH_3), 0.74 (3 H, s, *tert*-CH_3); δ_C (75 MHz; $CDCl_3$) 220.2, 72.5, 48.8, 47.2, 43.9, 43.5, 42.4, 30.8, 29.0, 19.9, 15.1, 13.0, 7.8; HRMS *m*/*z* for $C_{13}H_{22}O_2$ (Calc.: *M,* 210.1619. Found: M^+, 210.1605).

(1*R*,2*R*,3*R*,6*R*,7*S*)-(+)-1,2,6,7-Tetramethylbicyclo[4.3.0]nonan-3-ol 21

Modified Wolff–Kishner reduction of the keto alcohol **20** (25 mg, 0.0765 mmol) with hydrazine monohydrate (0.08 ml, 1.585 mmol) in a mixture of diethylene glycol (0.8 ml) and ethylene glycol (0.2 ml), and a solution of sodium (65.8 mg, 2.86 mmol) in diethylene glycol (1.32 ml), as described for 10-methylenepinguisane **6**, furnished the alcohol **21** (16 mg, 69%), $[\alpha]_D^{24}$ +3.4 (*c* 1.2, $CHCl_3$); ν_{max} (neat) 3340 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 3.31 (1 H, d of t, *J* 10.8 and 4.5 Hz, C*H*OH), 2.4 (1 H, q, *J* 6.9 Hz), 1.10–1.90 (10 H, m), 0.95 (3 H, d, *J* 6.6 Hz) and 0.81 (3 H, d, *J* 6.9 Hz) (together 2 × *sec*-CH_3), 0.77 (3 H, s) and 0.62 (3 H, s) (together 2 × *tert*-CH_3); δ_C (75 MHz; $CDCl_3$) 73.6, 41.7, 35.0, 34.5, 30.7, 29.2, 28.9, 19.0, 15.5, 14.6, 12.8; HRMS *m*/*z* for $C_{13}H_{24}O$ (Calc.: *M,* 196.1828. Found: M^+, 196.1814).

(1*R*,2*R*,6*R*,7*S*)-(−)-1,2,6,7-Tetramethylbicyclo[4.3.0]nonan-3-one 4

To a solution of the alcohol **21** (15 mg, 0.075 mmol) in methylene dichloride (0.5 ml) were added PCC (40 mg, 0.186 mmol) and silica gel (40 mg) and the mixture was stirred for 2 h, filtered through a silica gel column, and the column, was eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica gel column, using ethyl acetate–hexane (1:40) as eluent, furnished the Schinzer's ketone (−) **4** (14 mg, 92%) as an oil, which was identified by comparison of the spectral data with that of the racemic sample **4**;[4,8] $[\alpha]_D^{23}$ −38 (*c* 1, $CHCl_3$); ν_{max} (neat) 1715 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.59 (1 H, q, *J* 6.5 Hz, H-2), 2.35–2.55 (2 H, m, H_2-4), 2.16 (1 H, ddd, *J* 15.5, 5.1 and 3.8 Hz), 1.65–2.00 (2 H, m), 1.61 (1 H, ddd, *J* 14.1, 12.6 and 5.1 Hz), 1.25–1.50 (3 H, m), 0.95 (3 H, d, *J* 6.6 Hz) and 0.945 (3 H, d, *J* 6.8 Hz) (together 2 × *sec*-CH_3), 0.719 (3 H, s) and 0.717 (3 H, s) (together 2 × *tert*-CH_3); δ_C (50 MHz; $CDCl_3$) 214.1, 53.3, 48.4, 45.6, 37.7, 37.4, 35.5, 32.4, 29.2, 18.4, 16.5, 14.8, 8.7; *m*/*z* 194 (M^+, 20%), 179 (25), 137 (15), 123 (45), 122 (25), 109 (100).

(1*R*,2*R*,3*R*,6*R*,7*S*)-(+)-Pinguisenol 1

To a cold (−10 °C) magnetically stirred solution of the ketone **4** (12 mg, 0.062 mmol) in THF (2 ml) was added vinylmagnesium bromide [prepared from magnesium (4.4 mg, 0.185 mmol) and vinyl bromide (0.026 ml, 0.37 mmol) in THF (0.5 ml)] and the solution was stirred for 2 h at the same temperature. The reaction was then quenched with aq. NH_4Cl and extracted with diethyl ether. The organic layer was washed successively with water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column, using ethyl acetate–hexane (1:20) as eluent furnished pinguisenol (+)-**1** (11 mg, 80%) as a colourless oil, $[a]_D^{25}$ +22.5 (*c* 2, $CHCl_3$); ν_{max} (neat) 3610, 3480, 1640, 920 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.79 (1 H, dd, *J* 17.2 and 10.7 Hz), 5.17 (1 H, dd, *J* 17.2 and 1.2 Hz), 5.0 (1 H, dd, *J* 10.7 and 1.2 Hz), 2.20–2.40 (1 H, m), 1.80–1.55 (5 H, m), 1.53 (1 H, q, *J* 7.0 Hz), 1.30–1.10 (3 H, m), 0.95 (3 H, s, *tert*-CH_3), 0.83 (3 H, d, *J* 6.2 Hz) and 0.81 (3 H, d, *J* 6.7 Hz) (together 2 × *sec*-CH_3), 0.68 (3 H, s, *tert*-CH_3). δ_C (100 MHz; $CDCl_3$) 147.8, 110.7, 76.6, 47.3, 45.2, 40.6, 36.4, 34.1, 33.8, 29.4, 26.2, 19.3, 17.9, 14.6, 10.1.

Acknowledgements

We thank Professor Y. Asakawa, Tokushima Bunri University, for sending a sample of natural pinguisenol, and Professor Schinzer, Universitat Braunschweig, for sending copies of the spectra of bicyclic ketone (±)-**4**. We are grateful to the Council of Scientific and Industrial Research, New Delhi, for providing a research fellowship to D. V. K.

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