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Enantiospecific Synthesis of (+)-Pinguisenol, (+)-Pinguisen-10-one and (–)-Pinguisen-8,10-dione[1]

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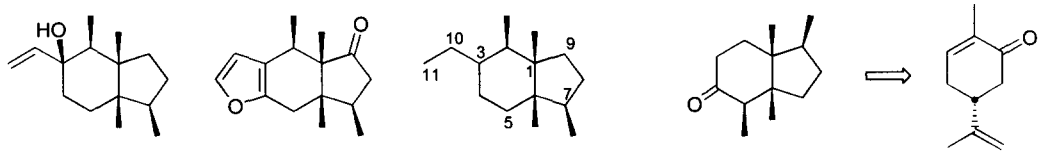
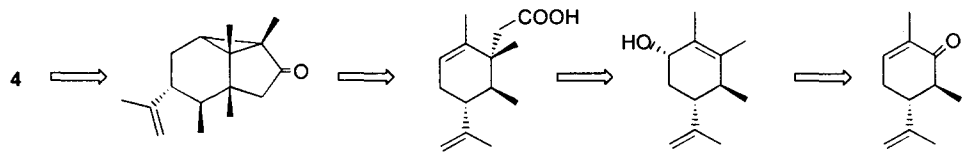
Abstract: The first enantiospecific total synthesis of the sesquiterpene (+)-pinguisenol, the optical antipode of the natural product, and the analogues (–)-pinguisen-10-one and (+)-pinguisen-8,10-dione, starting from R-carvone are described.

Pinguisenol (**1**), belonging to the pinguisane group of sesquiterpenes, was isolated[2] from the liverwort *Porella vernicosa* and *P. Densifolia* along with four other pinguisanes. The pinguisanes which, since the first isolation[3] of pinguisone (**2**) have steadily grown in number to more than twenty five,[4] contain an interesting irregular sesquiterpene carbon skeleton, 3-ethyl-1,2,6,7-tetramethylbicyclo[4.3.0]nonane (**3**) incorporating two vicinal quaternary carbon atoms and four methyl groups on four contiguous carbon atoms oriented in an all *cis* fashion, making them challenging synthetic targets. The structure of pinguisenol **1** was established on the basis of chemical and spectral studies and was confirmed by the total synthesis of (±)-**1**, by Schinzer *et al.*[5a] Recently, we reported[5b] a formal total synthesis of racemic pinguisenol (**1**) *via* the Schinzer's precursor **4**. In continuation, herein we describe the first enantiospecific total synthesis of (+)-pinguisenol, the optical antipode of the natural compound, along with several other analogues of the pinguisanes, starting from R-carvone (**5**).



1 **2** **3** **4** **5**

It was anticipated that the isopropenyl group could serve as a masked oxygen functionalilty. The retro-synthetic analysis of the bicyclic ketone **4** identified the tricyclic ketone **6**, the γ,δ-unsaturated acid **7** and the allyl alcohol **8** as the key intermediates with *trans*-6-methylcarvone[6] **9** as the starting material. First attention was focused on the synthesis of the tricyclic ketone **6**, Scheme 1. The requisite starting material methylcarvone **9** was obtained in a stereochemically pure form by kinetic alkylation[7] of carvone **5** using lithium diisopropylamide (LDA) and methyl iodide followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalysed equilibration of the resultant 3:2 epimeric mixture of 6-methylcarvone and crystallisation. To incorporate the three methyl groups on



6 **7** **8** **9**

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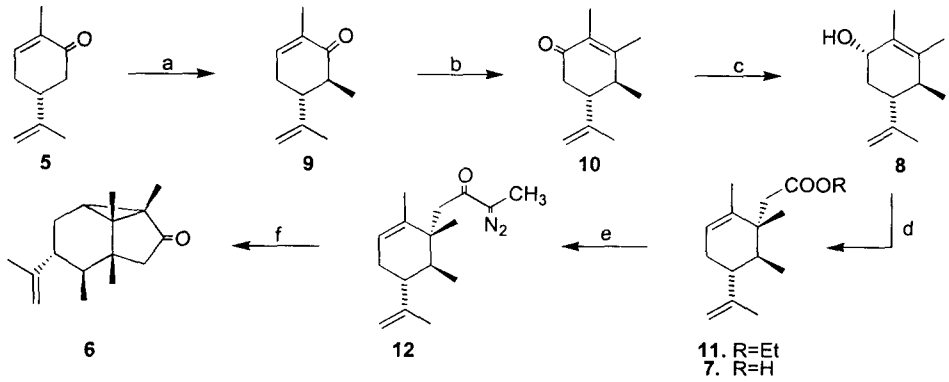
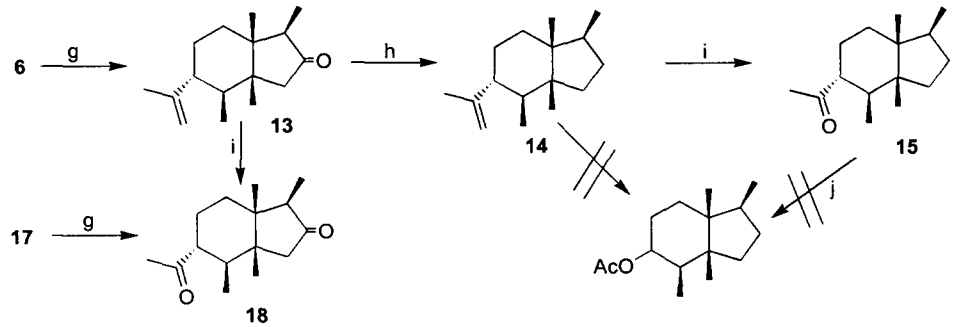


***Scheme 1: Reagents, Conditions and Yields**: (a) i. LDA, THF; MeI, -10 °C, 98%; ii. DBU, CH_2Cl_2, rt, 24 h, 95%; iii. crystallisation (hexanes); (b) i. MeMgI, Et_2O, 3 h; ii. PCC-silica gel, CH_2Cl_2, 3 h; 74% (2 steps); (c) LAH, Et_2O, -78 °C, 83%; (d) i. $MeC(OEt)_3$, EtCOOH (catalytic), sealed tube, 175 °C, 5 days, 65%; ii. 10% aq. NaOH, MeOH, reflux, 4 h, 92%; (e) i. $(COCl)_2$, C_6H_6, rt, 2 h; ii. CH_3CHN_2, Et_2O, 0 °C, 2 h; (f) an. $CuSO_4$, c-C_6H_{12}, tungsten lamp, reflux, 4 h; 52% from acid 7.*

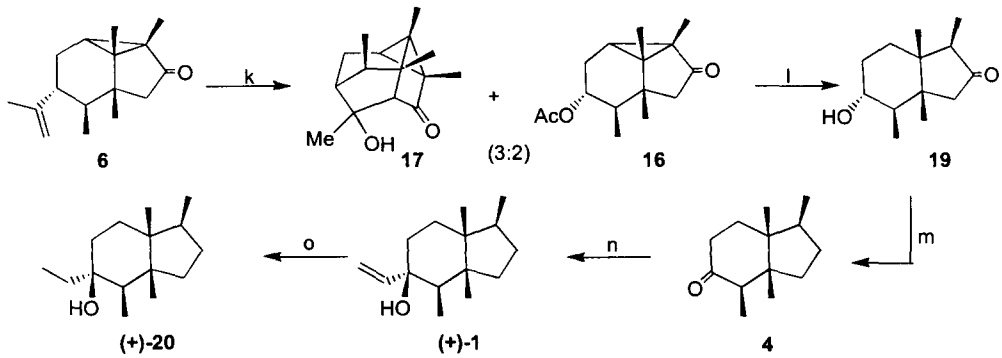
contiguous carbon atoms, the methylcarvone **9** was transformed into *trans*-3,4-dimethylcarvone (**10**) employing an alkylative 1,3-enone transposition. Thus, 1,2-addition of methylmagnesium iodide to methylcarvone **9** followed by oxidation of the resulting allylic *tert*-alcohol with pyridinium chlorochromate (PCC)-silica gel furnished *trans*-3,4-dimethylcarvone (**10**). A Claisen rearrangement based protocol was contemplated for the stereoselective creation of the first quaternary carbon atom. Thus, reduction of the enone **10** using lithium aluminium hydride (LAH) at low temperature furnished the allyl alcohol **8** with an excellent regio- and stereoselectivity, as both the C-4 and C-5 substituents direct the incoming hydride *anti* to C-5 isopropenyl group.[8] An orthoester variant of the Claisen rearrangement was employed for the stereospecific generation of the first quaternary carbon atom. Thus, heating the allyl alcohol **8** in triethyl orthoacetate in the presence of a catalytic amount of propionic acid, in a sealed tube, furnished the ester **11**, which on base catalysed hydrolysis generated the acid **7**. Since the hydroxy group and the secondary methyl group were *trans* oriented in the starting allyl alcohol **8**, the two methyl groups on the vicinal carbon atoms will automatically be *cis* oriented in the acid **7** as required for further elaboration. For the stereospecific creation of the second quaternary carbon atom, an intramolecular diazo ketone cyclopropanation reaction was employed. It was contemplated that cyclopropanation of the diazo ketone **12** derived from the acid **7** and diazoethane will also incorporate the requisite fourth methyl group on the fourth contiguous carbon atom. Consequently, treatment of the acid **7** with oxalyl chloride in benzene furnished the corresponding acid chloride which on treatment with an excess of ethereal diazoethane generated the diazo ketone **12**. Anhydrous copper sulfate catalysed decomposition of the diazo ketone **12** in refluxing cyclohexane (using a tungsten lamp) led to the cyclopropanated compound **6**, $[\alpha]_D^{24}$ +27.9 (c 3.8, $CHCl_3$), *via* stereo- and regiospecific insertion of the intermediate keto carbenoid from the *syn* face of the ring olefin generating the requisite carbon framework with four methyl groups on four contiguous carbon atoms in an all *cis* fashion.

After successfully synthesising the tricyclic ketone **6**, attention was turned towards its elaboration to pinguisanes. For the conversion of the tricyclic ketone **6** into the bicyclic ketone **4**, cyclopropane ring cleavage, deoxygenation and degradation of the isopropenyl group sequence was contemplated, Scheme 2. Regiospecific reductive cleavage[9] of the cyclopropane ring employing lithium in liquid ammonia transformed the tricyclic ketone **6**, exclusively into one isomer of the bicyclic ketone **13**, $[\alpha]_D^{27}$ -20 (c 1.2, $CHCl_3$) whose structure was assigned to be that of the thermodynamic product. The ketone **13** contains the complete stereochemical carbon framework of pinguisanes, *i.e.*, compound **13** is 10-methylenepinguisen-8-one. Huang-Minlon modified Wolff-Kishner reduction of the ketone **13** generated the deoxygenated compound, 10-methylenepinguisene **14**. Since a



***Scheme 2*: Reagents, Conditions and Yields**: *(g) Li, liq. NH_3, 0.5 h, 81% for **13**; 70% for **18**; (h) NH_2NH_2, digol, $(CH_2OH)_2$, 180 °C, 2h; Na in digol, 180 °C, 4 h; 70%; (i) O_3/O_2, MeOH:CH_2Cl_2 (1:4), -70 °C; Me_2S, rt, 12 h; 68%; (j) m-CPBA, TFA, CH_2Cl_2, rt, 24 h.*

direct ozonation-Criegee rearrangement[10] was not successful for the conversion of the isopropenyl group into an acetoxy group in the hydrindane **14**, a step wise sequence was adopted. Ozonolysis followed by reductive work up transformed the hydrindane **14** into pinguisen-10-one **15**.[11] For the formation of the ketone group from the acetyl group in **15**, a Baeyer-Villiger based strategy was attempted. Even though it was successful on a model system which lacks the C-2 methyl group, the pinguisenone **15** failed to provide the oxidation product even under forcing conditions. This unexpected failure forced us to modify the sequence, and degradation of the isopropenyl group was carried out at an earlier stage of the sequence, which is depicted in scheme 3. Ozonation of the tricyclic compound **6** in 1:5 methanol-methylene chloride followed by Criegee rearrangement[10] of the intermediate methoxyhydroperoxide using acetic anhydride, triethylamine and 4-dimethylaminopyridine (DMAP) in refluxing benzene furnished a 2:3 mixture of the Criegee product, acetoxy ketone **16** and the hydroxy ketone **17**,[11] which was separated on a silica gel column. The hydroxy ketone **17**, which was found to be predominantly one epimer, was obviously formed *via* the intramolecular aldol reaction of the direct ozonolysis product under the basic conditions of the reaction. The regiospecific cyclopropane ring cleavage using lithium in liquid ammonia transformed the hydroxy ketone **17** into pinguisen-8,10-dione[11] **18**, which was found to be identical to the product obtained by ozonolysis of the bicyclic ketone **13** (Scheme 2). Regiospecific cyclopropane ring cleavage and concomitant hydrolysis of the acetoxy ketone **16** using lithium in liquid ammonia furnished the hydroxy ketone **19**. Huang-Minlon modified Wolff-Kishner reduction followed by oxidation with PCC transformed the hydroxy ketone **19** into the bicyclic ketone **4**, $[\alpha]_D^{23}$ -38 (c 1, $CHCl_3$), the precursor to pinguisenol, which exhibited spectral data identical to that of the racemic compound prepared earlier by Schinzer *et al.* and our group.[5] Finally, addition



***Scheme 3*: Reagents, Conditions and Yields**: *(k) i. O_3/O_2, MeOH:CH_2Cl_2 (1:4), -70 °C; ii. Ac_2O, NEt_3, DMAP, C_6H_6, reflux; 77%; (l) Li, liq. NH_3, 0.5 h, 80%; (m) i. NH_2NH_2, digol, $(CH_2OH)_2$, 180 °C, 2h; Na in digol, 180 °C, 4 h; ii. PCC, silica gel, CH_2Cl_2, 2 h; 64% (2 steps); (n) CH_2=CHMgBr, THF, -10 to 0 °C, 2 h, 80%; (o) H_2, 10% Pd-C, MeOH, 2 h, 90%.*

of vinylmagnesium bromide to the bicyclic ketone **4** furnished (+)-pinguisenol **1**, $[\alpha]_D^{25}$ +22.5 (c 2, $CHCl_3$), which exhibited ^1H NMR (300 MHz) spectrum identical to that of the natural pinguisenol.[12] To confirm the absolute stereochemistry, our synthetic pinguisenol was hydrogenated using 10% Pd over carbon as the catalyst to furnish (+)-dihydropinguisenol **20**, $[\alpha]_D^{25}$ +23.3 (c 0.7, $CHCl_3$), which established that our synthetic pinguisenol as the optical antipode of the natural product.[2]

In conclusion, we have achieved the first enantiospecific total synthesis of (+)-pinguisenol establishing the absolute stereochemistry of the natural compound as *1S,2S,3R,6S,7R*. In addition, the present strategy provided several analogues of pinguisenes, *e.g.*, pinguisen-8-one; pinguisen-8,10-dione; 10-methylenepinguisene; 10-methylenepinguisen-8-one.

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References and Notes

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11. All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR) consistent with their structures. Spectral data for select compounds are as follows: For the pinguisen-10-one **15**: $[\alpha]_D^{29}$ 14.2 (c 3.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1705; ^1H NMR (300 MHz, $CDCl_3$): δ 2.50-2.20 (1 H, m), 2.13 (3 H, s), 2.10-1.20 (10 H, m), 0.87 (3 H, d, *J* 6.3 Hz), 0.83 (3 H, s), 0.71 (3 H, d, *J* 5.5 Hz), 0.68 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 Calcd. for $C_{15}H_{26}O$ 222.1984; Found 222.1970. For the acetoxy ketone **16**, $[\alpha]_D^{24}$ +3.8 (c 1.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1735, 1715; ^1H NMR (400 MHz, $CDCl_3$): δ 4.72 (1 H, ddd, *J* 12, 7.2 & 4.9 Hz), 2.43 (1 H, ddd, *J* 15.6, 8.9 & 7.4 Hz), 2.26 (1 H, d, *J* 19.6 Hz), 2.17 (1 H, d, *J* 19.6 Hz), 2.03 (3 H, s), 1.70-1.60 (2 H, m), 1.24 (3 H, s), 1.22 (3 H, s), 1.17 (3 H, s), 1.20-1.15 (1 H, m), 1.09 (3 H, d, *J* 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 Calcd. for $C_{15}H_{22}O_3$ 250.1569; Found 250.1555. For the hydroxy ketone **17**, $[\alpha]_D^{26}$ +7.2 (c 3.2, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3450, 1700; ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (1 H, d, *J* 15 Hz), 1.94 (1 H, t of d, *J* 15 & 6.2 Hz),1.90 (1 H, s), 1.88 (1 H, s), 1.74 (1 H, d of q, *J* 6.9 & 4.1 Hz), 1.70-1.60 (1 H,m), 1.32 (3 H, s), 1.19 (3 H, s), 1.14 (3 H, d, *J* 6.8 Hz), 1.14 (3 H, s), 1.10 (3 H, s), 1.04 (1 H, d, *J* 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 Calcd. for $C_{15}H_{22}O_2$ 234.1620; Found 234.1621. For the pinguisene-8,10-dione **18**: $[\alpha]_D^{29}$ -8.8 (c 2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1730, 1705. ^1H NMR (300 MHz, $CDCl_3$): δ 2.80 (1 H, q, *J* 6.9 Hz), 2.43 (1 H, m), 2.33 (1 H, d, *J* 19.5 Hz), 2.16 (3 H, s), 1.99 (1 H, d, *J* 19.5 Hz), 1.86 (1 H, q of d, *J* 13.2 & 6.6 Hz), 1.70-1.50 (4 H, m), 0.98 (3 H, s), 0.92 (3 H, d, *J* 6.9 Hz), 0.80 (3 H, d, *J* 6.4 Hz), 0.76 (3 H, s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 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). Mass: m/z 236 (M^+, $C_{15}H_{24}O_2$, 16%), 221 (100), 121 (78), 109 (56).
12. Other spectral data was found to be identical to that reported for the racemic compound.[5a]