Tetrahedron Letters,Vol.24,No.16,pp 1749-1752,1983 0040-4039/83/161749-04$03.00/0
Printed in Great Britain

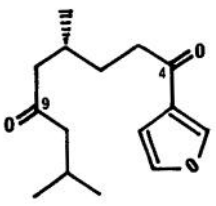
FURTHER SKELETAL VARIETY IN THE TOXIC FURANOSESQUITERPENE KETONES IN THE *MYOPORUM* GENUS

Pierre L. Métra and Maurice D. Sutherland*

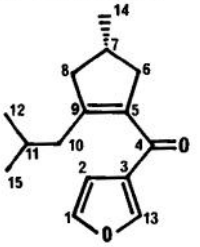
Chemistry Department, University of Queensland, Brisbane 4067, Australia

Summary: Two 'new' furanosesquiterpene ketones, (+)-myomontanone [4S-(β-furanyl)[4-methyl-2-(2'-methylpropyl)cyclopent-1-en-1-yl]methanone] and the corresponding endocyclic β,γ-enone constitute 70% and 3% of the essential oil of the leaves of Myoporum montanum, *and are shown to be the kinetic aldol condensation products of (+)-myoporone, also present (22%) in the oil.*

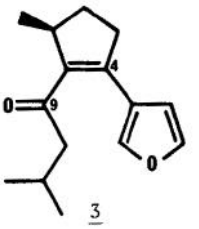
A sample of the leaves of the inland Australian shrub *Myoporum montanum(?)* (Myoporaceae family) was submitted to us from a Western Australian source for prediction of its stock-poisoning potential from its content of toxic furanosesquiterpenes.[1,2,3,4,5,6] The leaves yielded 1.25% of essential oil which contained two 'new' ketones, (+)-myomontanone (70%) and isomyomontanone (3%), the known diketone (+)-myoporone[4,7] 1 (22%), sesquiterpene hydrocarbons and alcohols (3%), palmitic acid (1%) and traces of other substances.



1



2



3

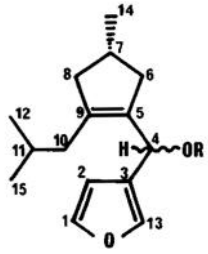
(+)-S-Myomontanone† 2, m.p. 45°, b.p. 109°/1 mm, $[\alpha]_D$ +26° (c 3.5 in $CHCl_3$/2% EtOH) separated from the cold oil and from isooctane as colourless needles. While 2 is very similar to (-)-S-myodesmone[2] 3 from *M. deserti* and *M. acuminatum* on various g.l.c. phases (including B34/DEGS),[6] it is just separated by a 50m OV101 capillary column at 145° but not at 190°. A clear distinction between the two isomeric conjugated ketones is readily provided by gc/ms.‡

† 2: Found: C, 77.4; H. 8.75; required for $C_{15}H_{20}O_2$: C, 77.6; H. 8.6%. I.r. in $CHCl_3$; ν: 3140, 3010, 2960, 2935, 2875, 1635, 1560, 1510, 1450, 1160, 875, 835, 770 cm^{-1}. Gc/ms; m/e: 232 (18), 217 (51), 203 (42), 189 (32), 161 (83), 95 (100%). 100 MHz-^{1}H n.m.r. in $CDCl_3$; δ (ppm/TMS): 0.81 and 0.83, both (3H, d, 7 Hz) & non-equivalent due to chirality about C-7; 1.07 (3H, d, 6.5 Hz); 1.80-2.82 (8H, complex); 6.76 (1H, dd, 1.9 and 0.8 Hz); 7.38 (1H, dd, 1.9 and 1.45 Hz); 7.88 (1H, dd, 1.45 and 0.8 Hz). 25.05 MHz-^{13}C n.m.r. in $CDCl_3$; δ (ppm/TMS): 21.12 (q, C-14); 22.49 and 22.73 (q, C-12 and C-15); 27.35 (d, 123 Hz, C-11); 31.56 (d, 134 Hz, C-7); 39.31 (t, 127 Hz, C-10); 43.70 (t, 130 Hz, C-8); 45.54 (t, 130 Hz, C-6); 109.49 (d, 179 Hz, C-2); 128.50 (s, C-3); 136.34 (s, C-9); 143.59 (d, 204 Hz, C-1); 147.37 (d, 204 Hz, C-13); 152.84 (s, 5C); 189.20 (s,4C) (farnesol numbering throughout).

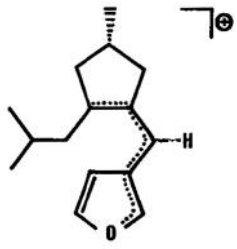
‡ Hewlett Packard HP 5592B: correlation index 0.124.

The molecular formula $C_{15}H_{20}O_2$ for 2 was confirmed by the fifteen lines of the ^{13}C n.m.r. spectrum and the molecular ion m/e 232. The electronic spectrum in EtOH shows a maximum (ε 7000) at 271 nm suggesting a conjugated α,β-enone also responsible for the strong infrared band at 1635 cm^{-1}. A furan ring provides characteristic[8] infrared bands and a β-furyl ketone absorption[8] (ε 11000) at 207 nm which is supported by the mass spectral fragment m/e 95 (base peak). The field positions and fine coupling of three ring protons in the ^1H n.m.r. spectrum indicate the substitution pattern of the furan moiety. The ^{13}C n.m.r. spectrum shows six sp^2 carbon signals as three doublets (furan ring) and three singlets in agreement with the absence of olefinic protons from the n.m.r. spectrum. Finally, the three methyl doublets require the plane structure of 2 if the farnesyl skeleton is to be retained. The above structure was confirmed and the indicated absolute configuration established, by preparing (+)-myomontanone 2 from (+)-myoporone 1 as described on the next page.

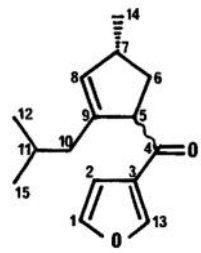
Selective reduction of the carbonyl group of 2 by $NaBH_4/CeCl_3$[10] in methanol yielded a mixture of methyl ethers, mainly 4, the oily alcohol* 5 being obtained only by a 2 hr reduction in t-BuOH/DMSO (1:1 by volume). Myomontanol* 5, b.p. 60°/0.01 mm (kugel-rohr), which showed hydroxyl absorption at 3600 cm^{-1} and a singlet proton signal at 5.52 ppm, was converted to 4^+ in one hour by treatment with $MeOH/H_2O$ acidified to pH 4 (glass electrode). The labile nature of 4 and the formation of two g.l.c. peaks of the same low retention from both 4 and 5, presumably result from extensive delocalisation of the cation 6.



4 R = CH_3
5 R = H



6



7

---

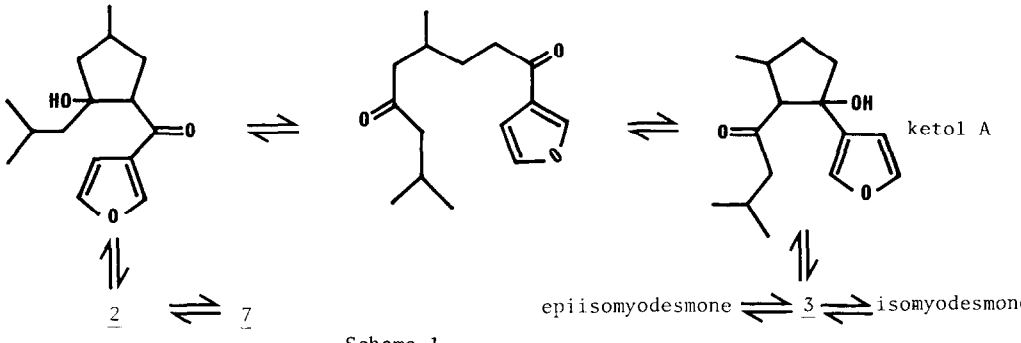
* 5: Purification by preparative t.l.c. on silica gel using 5% ethyl acetate in hexane, R_f 0.12. Found: C, 76.9; H, 9.5; required for $C_{15}H_{22}O_2$: C, 76.9; H, 9.4%. I.r. in $CHCl_3$; ν: 3600, 2950, 2920, 1500, 1460, 1205, 1160, 1025, 875, 665 cm^{-1}. U.v. in EtOH; λ_{max} nm (ε_{max}): 209 (11,000); 271 (900). 100 MHz-^1H n.m.r. in $CDCl_3$; δ (ppm/TMS): 0.88 and 0.89, both (3H, d, 7 Hz); 1.02 (3H, d, 7 Hz); 1.4-2.8 (9H, complex including OH); 5.52 (1H, broad s); 6.28 (1H, m); 7.33 (2H, complex).

+ 4: R_f 0.61 (solvent mixture as for 5). 100 MHz-^1H n.m.r. in $CDCl_3$; δ (ppm/TMS): 3.3 (3H, s).

Isomyomontanone* 7 was formed to ∿18% from 2 by equilibrating for 3 hr with 0.3% KOH in refluxing 66% aqueous ethanol under nitrogen, and was separated as an oil from 2 on a Merck Lobar silica gel 60 column with 30% CH_2Cl_2 in hexane. Two stereoisomers with finely coupled vinyl proton signals in the ^1H n.m.r. spectrum[11] and appropriate ^{13}C spectra could be distinguished. *M. montanum* oil yields a g.l.c. peak of retention and mass spectrum identical (correlation index 0.986) to 7 indicating that isomyomontanone is a natural substance.

(+)-Myoporone of $[\alpha]_D$+5° was isolated[4] from the *M. montanum* oil, and refluxed in methanolic KOH (1%) for ∿4 days at which time the concentration of myomontanone had reached its maximum (∿60% of the volatile products). The products were eluted from Lobar silica gel 60 columns (two in series) with 30% CH_2Cl_2 in hexane. The myomontanone was separated† from the myoporone, isomyomontanone, myodesmone (∿20%), isomyodesmone,[2] epiisomyodesmone[2] and other minor products, as needles m.p. and mixed m.p. 44°, $[\alpha]_D$ + 24° with the spectral characteristics of the natural substance 2. (Similarly (-)-myoporone $[\alpha]_D$ -3.7° from *M. betcheanum*[4] yielded (-)-myomontanone of m.p. 43° and $[\alpha]_D$ -14°). Hence the configuration of (+)-myomontanone 2 is related to that of (+)-R-myoporone 1, as would be expected from their co-occurrence in *M. montanum* oil.

Prolonged refluxing of the above reaction mixture however, leads to the eventual predominance of the myodesmone series to the virtual exclusion of the myomontanones as noted previously.[2,4] Hence myomontanone and myodesmone (and their equilibrating β,γ-enones) are identified as kinetic and thermodynamic products of competing *in vitro* intramolecular aldol condensations ‡ (see Scheme 1). In Nature however, distinct enzyme systems must be involved since *M. montanum* oil appears to be devoid of myodesmone just as the myodesmone-rich Jackson variety[2] of *M. deserti* is free of myomontanone although both oils contain myoporone (of opposite chirality).



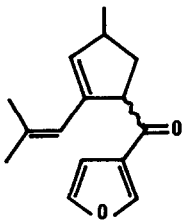
Scheme 1

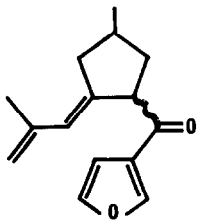
* 7: Gc/ms; m/e: 232 (9), 189 (15), 95 (100%). U.v. in EtOH; λ_{max} nm (ε_{max}): 215 (22,000); 252 (9,000). 100 MHz-^1H n.m.r. in $CDCl_3$; δ (ppm/TMS): 0.83 (6H, complex); 1.02 and 1.08 (3H, one d per diastereoisomer, 7 Hz); 1.64-2.84 (6H, complex); 3.92 (1H, m); 5.49 (1H, m); 6.78 (1H, dd); 7.41 (1H, dd); 8.05 (1H, dd). 75.46 MHz-^{13}C n.m.r. in $CDCl_3$; δ (ppm/TMS): ∿58 (C-5), ∿135 (C-8), ∿141 (C-9), all paired.

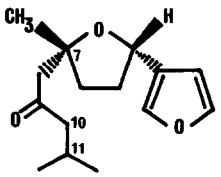
† Chromatographic data: R_t (50m cap. OV101, temperature program: 145° for 50 mn, 5° per mn to 190°)/R_f (silica 60 analytical plates, solvent 50% EtOAc in hexane/30% CH_2Cl_2 in hexane): myoporone 1.29|0.08|<0.05, myodesmone and isomyodesmone 1.01|0.47|0.28, myomontanone 1.00|0.38|0.17, epiisomyodesmone 0.95|0.47|0.28; isomyomontanone 0.93|0.38|0.22.

‡ By 'aldol condensation', we imply the aldol reaction followed by dehydration.

The occurrence of 2 and 7 in *M. montanum* reveals an additional furanosesquiterpene ketone carbon skeleton in the *Myoporum* genus, if not in *Eumorphia prostata* of the Compositae family from which Bohlmann and Zdero[11] isolated 8 and 9 in minute yields amongst other furanosesquiterpenes.

8: 

9: 

10: 

The fourteen previously recognised furanosesquiterpene ketones of *M. deserti*,[1,2,3,4,5] *M. acuminatum*,[2,4,12,13] *M. betcheanum*,[4,13] *M. bontioides*,[7] *M. laetum*,[14] *M. crassifolium*,[15] *M. tenuifolium*[15] *and M. tetrandrum*[15] include (+)- and (-)-myoporone,[4,7,15] (-)-10,11-dehydromyoporone[4,15] (farnesol numbering), members of the myodesmone series with[3] and without 10,11-unsaturation,[2] ketol A[13] (see Scheme 1), 10,11-dehydroketol A,[15] and five ngaionoid constituents including (-)-ngaione[1,14,15] (for which the absolute configuration 10 has been recently confirmed[6]), its 7-epimer,[15] both 10,11-unsaturated epimers,[5,15] and a C_{12} ketone (retro-aldol product?) lacking the isopropyl group of (-)-ngaione.

Those of the above substances that have been tested[16] have all been shown to be hepatotoxic in laboratory animals and stock. The toxicology of myomontanone is under examination by Dr. A.A. Seawright of the Veterinary School of the University of Queensland.

We wish to acknowledge technical assistance of V. Alberts, P. Barron, J.C. Kent, L. Lambert and others, and the award of a University of Queensland Postdoctoral Research Fellowship to one of us (P.L.M.). Funding by the Australian Research Grants Committee is acknowledged.

---

1. B.F. Hegarty, J.R. Kelly, R.J. Park and M.D. Sutherland, *Aust. J. Chem.*, 23, 107 (1970).
2. I.D. Blackburne, R.J. Park and M.D. Sutherland, *Aust. J. Chem.*, 24, 995 (1971).
3. I.D. Blackburne, R.J. Park and M.D. Sutherland, *Aust. J. Chem.*, 25, 1779 (1972).
4. I.D. Blackburne, R.J. Park and M.D. Sutherland, *Aust. J. Chem.*, 25, 1787 (1972).
5. W.D. Hamilton, R.J. Park, G.J. Perry and M.D. Sutherland, *Aust. J. Chem.*, 26, 375 (1973).
6. C.A. Russell and M.D. Sutherland, *Aust. J. Chem.*, 35, 1881 (1982).
7. T. Kubota and T. Matsuura, *Chemy Ind.*, 491 (1957); *Bull. Chem. Soc. Japan*, 31, 491 (1958).
8. T. Kubota (p.279) in Cyclopentanoid Terpene Derivatives, Ed. W.I. Taylor and A.R. Battersby, Marcel Decker Inc. New York (1969).
9. G. Magnusson and S. Thóren, *Tetrahedron*, 30, 1431 (1974) and references therein.
10. J.-L. Luche, L. Rodriguez-Hahn and P. Crabbé, *J.C.S. Chem. Comm.*, 601 (1978).
11. F. Bohlmann and L. Fiedler, *Chem. Ber*, 114, 227(1981); F. Bohlmann and C. Zdero, *Phytochemistry*, 17, 1155 (1978).
12. A.J. Birch, R. Massy-Westropp and S.E. Wright, *Aust. J. Chem.*, 6, 385 (1953).
13. J. Rodwell and M.D. Sutherland, unpublished results.
14. F.H. McDowall, *J. Chem. Soc.*, 127, 2200 (1925); 731 (1927); 1324 (1928).
15. M.D. Sutherland, unpublished results.
16. A.A. Seawright, J. Hrdlicka, J.S. Lee and E.A. Ogunsan, *J. of App. Toxicology*, 2, 75 (1982).

(Received in UK 4 January 1983)