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STEREOSPECIFIC SYNTHESIS OF THAPS-7(15)-ENE AND THAPS-6-ENE, PROBABLE BIOGENETIC PRECURSORS OF THAPSANES

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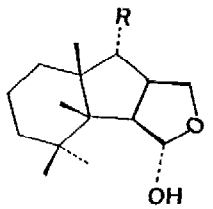
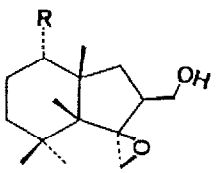
Abstract: Stereospecific synthesis of the title compounds, containing the basic carbocyclic skeleton of thapsanes, based on intramolecular diazoketone cyclopropanation reaction, is described.

Recently, a series of thapsanes, both hemiacetalic (1) and open form (2), has been isolated from the Mediterranean umbelliferous plant, Thapsia villosa var. minor.[1] A characteristic of the structure of this new class of sesquiterpenes is the presence of the unique 3a,4,4,7a-tetramethyl cis-hydrindane moiety incorporating three contiguous quaternary carbons. Our preliminary synthetic investigations towards thapsanes, based on the intramolecular diazoketone cyclopropanation reaction, resulted in the first stereospecific synthesis of thaps-7(15)-ene (13) and thaps-6-ene (14), probable biogenetic precursors[2] of these sesquiterpenes containing the basic carbocyclic framework thapsane 3, which is the subject of this communication.



1

R=OSen



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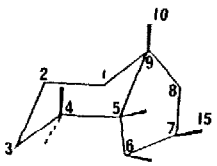
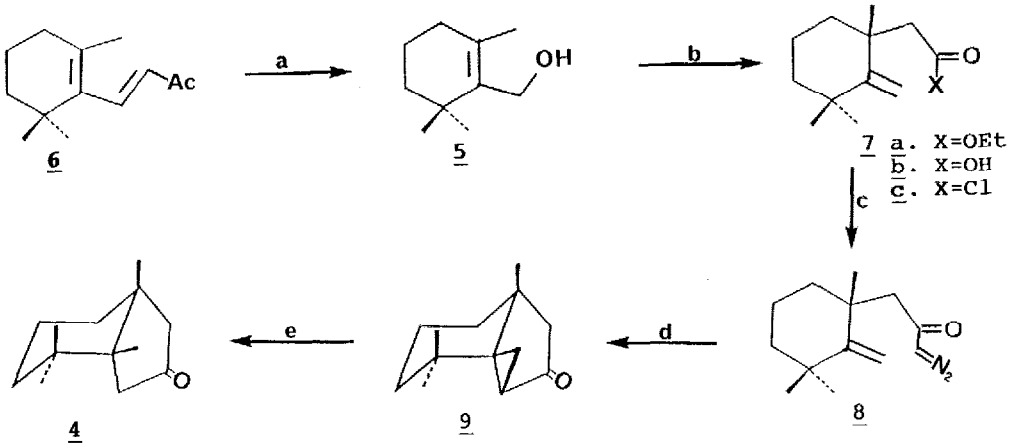


3

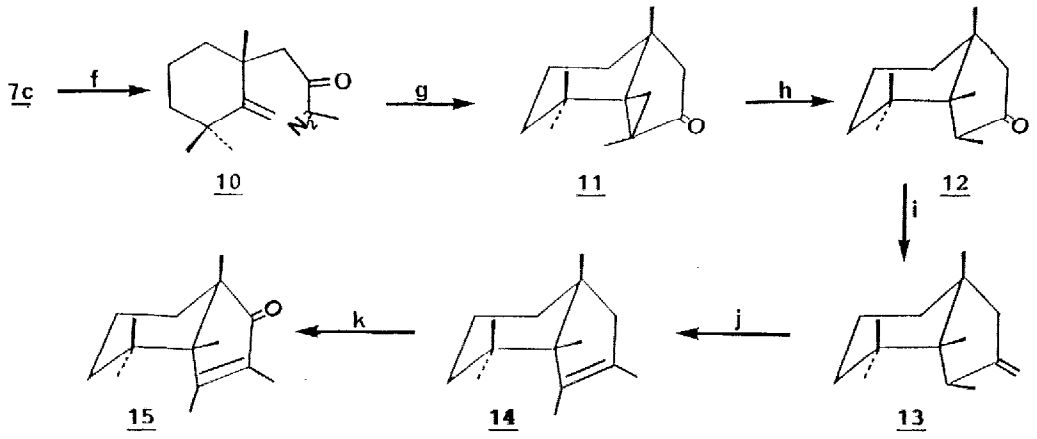
Initially, attention was paid to the stereospecific construction of the critical tetramethyl cis-hydrindanone 4 containing the requisite three contiguous quaternary carbons. The synthetic sequence is depicted in the Scheme 1. The starting cyclogeraniol (5) was obtained, in 60% yield, by selective ozonation[3] of the β-ionone (6), and direct reduction of the ozonide with sodiumborohydride. The ortho ester Claisen rearrangement[4] of the allylic alcohol 5 using triethyl orthoacetate in the presence of propionic acid (sealed tube, 180° C, 7 days), followed by base hydrolysis of the resultant ester 7a furnished, in 60% yield, the acid 7b.[5] Treatment of the acid chloride 7c, obtained from acid 7b and oxalyl chloride, with excess diazomethane generated the key diazoketone 8. Anhydrous copper sulphate



SCHEME 1: (a) i. O_3, MeOH, -70° C; ii. $NaBH_4$, -70° C-RT, 5 hr, 60%; (b) i. $MeC(OEt)_3$, EtCOOH, sealed tube, 180° C, 7 days; ii. 10% aq.NaOH, MeOH, reflux, 8 hr, 62%; (c) i. $(COCl)_2$, C_6H_6, RT, 6 hr; ii. CH_2N_2, Et_2O, RT, 4 hr; (d), anhydrous $CuSO_4$, C_6H_{12}, reflux, W-lamp, 4 hr, 40% from **7b**; (e) Li, liq. NH_3, 30 min, 65%.

catalysed decomposition[6] of the diazoketone **8** in cyclohexane (tungstun lamp) and intramolecular insertion of the resultant ketocarbene into the exomethylene, stereospecifically gave the cyclopropyl ketone **9**, a known degradation product of the sesquiterpene thujopsene.[7,8] Regiospecific cleavage of the cyclopropyl ketone **9**, using lithium in liquid ammonia reduction conditions, furnished cleanly the desired hydrindanone **4** with cis ring junction.[8,9]

Having achieved the synthesis of the ketone **4**, demonstrating the feasibility of the sequence, it was extended to complete the construction of the thapsane. However, further elaboration of **4** posed serious regiochemical problems as the two methylenes α to carbonyl in **4** are not easily distinguishable. To over come this, the sequence was slightly altered and used diazoethane instead of diazomethane as depicted in the scheme 2. Thus, treatment of the acid chloride **7c** with excess diazoethane[10] in ether furnished the diazoketone **10**. Decompostion of the diazoketone **10** under standard conditions as described above, provided the cyclopropyl ketone **11**, whose structure is clearly delineated from its spectral data.[8] Regiospecific cleavage of the cyclopropyl ketone **11** (Li-liq. NH_3) furnished a ketone, for which the thermodynamically favourable structure **12** was proposed, based on its inertness towards further equilibration conditions.[8,11] Wittig olefination of the ketone **12** resulted the thaps-7(15)-ene (**13**). Isomerisation of the exo cyclic olefin using p-toluene sulfonic acid furnished the thaps-6-ene (**14**). Structures of the olefins **13** and **14** were established from their spectral data



SCHEME 2: (f) $MeCHN_2$, Et_2O, RT, 4 hr; (g) Anhydrous $CuSO_4$, C_6H_{12}, reflux, W-lamp, 4 hr, 31% from **7b**; (h) Li, liq.NH_3, 30 min, 73%; (i) $Ph_3P^+CH_3\ ^-Br$, $^tamO^-\ ^+K$, C_6H_6, RT, 4 hr, 66%; (j) CH_2Cl_2, pTSA, RT, 5 hr, 80%; (k) 70% ^tBuOOH, CrO_3, CH_2Cl_2, 5 hr, 20%.

and further confirmation came through the oxidation of **14**. Oxidation of the olefin **14** using[12] t-BuOOH and CrO_3 furnished the enone **15**, which exhibited the ^1H NMR spectrum identical to that reported[1] for the degradation product of the thapsane **1**.

In conclusion, we have reported here a stereospecific synthesis to two thapsanes, **13** and **14**, using the copper catalysed intramolecular cyclopropanation reaction of diazoketones. Currently, this work is being extended towards the synthesis of functionalised thapsanes, like **1** and **2**.

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REFERENCES AND NOTES

1. Teresa, P.J., Moran, J.R. and Grande, M., Chem. Lett., **1985**, 865; Teresa, P.J., Moran, J.R., Fernandez, A. and Grande, M., Phytochemistry, **1986**, 25, 703 and 1171.
2. Even though these olefins are not isolated so far from nature, from the literature precedence of isolation of hydrocarbons much later than the derivatives, we strongly believe that either one or both of these olefins will be isolated in due course.
3. Jalali-Naini, M., Guillerm, D. and Lallemand, J.Y., Tetrahedron, **1983**, 39, 749.
4. Johnson, W.S., Werthermann, L., Bartlett, W.R., Brocksom, T.J., Li.T., Faulkner, D.J. and Peterson, M.R., J. Am. Chem. Soc., **1970**, 92, 741.
5. Mc Murry, J.E. and Blaszczak, L.C., J. Org. Chem., **1974**, 39, 2217; Branca, S.J., Lock, R.L. and Smith, A.B., J. Org. Chem., **1977**, 42, 3165.
6. Tahara, A., Shimagaki, M., Ohara, S. and Nakata, T., Tetrahedron Lett., **1973**, 14, 1701.

7. Forsen, S. and Norin, T., Acta Chem. Scand., **1961**, 15, 592; Sekizaki, H., Ito, M. and Inoue, S., Bull. Chem. Soc. Japan, **1978**, 51, 2439.
8. Selected spectral data: for **8**; IR (neat), 2100, 1630 cm^{-1}; for **9**; mp. 118-121° C (lit.[7] 122° C); IR (nujol), 3050, 1725 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 0.63 (3H,s), 1.15 (3H,s), 1.23 (3H,s), 0.9-2.2 (11H,m); ^{13}C NMR (22.5 MHz, $CDCl_3$), 212.9(s), 49.8(t), 46.1(s), 39.8(t), 39.5(t), 38.1(s), 35.0 (d), 31.4(s), 27.5(q), 27.1(q), 23.3(q), 18.5(t), 15.4(t); for **4**: mp. 124-127°C (lit.[9] 171-175° C), 2,4-DNP mp. 171-173°C (lit.[9] 125-127°C); IR (nujol), 1745 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$), 2.65 (1H,d,J=18.5Hz), 2.35 (1H,d,J=18.8Hz), 1.92 (1H,d,J=18.8Hz), 1.88 (1H,d,J=18.5Hz), 1.7-1.2 (6H, m), 1.19 (3H,s), 1.06 (3H,s), 1.01 (3H,s), 0.83 (3H,s); ^{13}C NMR (22.5 MHz, $CDCl_3$), 218.1(s), 54.3(t), 49.3(t), 45.8(s), 40.6(s), 37.3(2C,t), 34.8(s), 28.1(q), 24.7(q), 22.2(q), 18.4(t), 18.1(q); HRMS, $C_{13}H_{22}O$ required 194.1671, obtained 194.1681; for **10**: IR (neat), 2060, 1630 cm^{-1}; for **11**: mp. 116-120° C, IR (neat), 1725 cm^{-1}; ^1H NMR (90 MHz,$CDCl_3$), 0.88 (3H,s), 1.2 (3H,s), 1.24 (3H,s), 1.42 (3H,s), 1.0-1.8 (9H,m), 2.08 (1H,1/2 AB,J=18H); ^{13}C NMR (22.5 MHz, $CDCl_3$), 214.1(s), 49.4(t), 41.9(s), 40.3(t), 39.6(t), 37.9(s), 34.0 (s), 28.9(2C,q), 23.5(q), 22.1(t), 18.7(t), 14.2(q); HRMS, $C_{14}H_{22}O$ required 206.1671, obtained 206.1666; for **12**: mp.119-123° C, IR (nujol), 1740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$), 2.61 (1H,q,J=7.2Hz), 2.26 (1H,d,J=18.2Hz), 1.9 (1H,d,J=18.2Hz), 1.7-1.2 (6H,m), 1.21 (3H,s), 1.1(3H,d,J=7.2Hz), 1.04 (3H,s), 0.88 (6H,s); ^{13}C NMR (22.5 MHz, $CDCl_3$), 221.4(s), 54.0(t), 48.8(d), 48.1(s), 39.8(s), 37.9(t), 37.4(t), 36.3(s), 29.7(q), 25.5(q), 22.9(q), 18.5(t), 13.4(2C,q); HRMS, $C_{14}H_{24}O$ required 208.1827, obtained 208.1825; for **13**: IR (neat), 1650 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$), 4.83 (2H,brs), 2.8 (1H,m), 2.43 (1H,dq,J=17,3Hz), 1.92-1.0 (7H,m), 1.12 (3H,d,J=7Hz), 1.1 (3H,s), 1.0 (3H,s), 0.9 (3H,s), 0.8 (3H,s); ^{13}C NMR (22.5 MHz, $CDCl_3$), 157.5(s), 105.7(t), 49.7(t), 49.4(s), 42.7(s), 42.5(d), 38.4(t), 36.5(t), 36.3(s), 30.0(q), 25.4(q), 23.1(q), 19.0(t), 18.4(q), 13.1(q); for **14**: IR 1460, 1385 cm^{-1},^1H NMR (90 MHz, $CDCl_3$), 2.38 (1H,br d,J=17Hz), 1.58 (6H,s), 1.05-1.7 (7H,m), 0.92 (6H,s), 0.84 (3H,s), 0.76 (3H,s); ^{13}C NMR (22.5 MHz, $CDCl_3$), 136.2, 130.0, 55.0, 50.7, 43.8, 38.4, 37.6, 35.1, 30.9, 30.5, 27.1, 18.7, 15.0, 14.1, 13.0; HRMS, $C_{15}H_{26}$ required 206.2034, obtained 206.2058.
9. Norin, T., Acta Chem. Scand., **1963**, 17, 738; The melting points reported for the ketone **4** and its 2,4-DNP derivative, we believe, were interchanged in this manuscript.
10. Marshall, A. and Patridge, J.J., J. Org. Chem., **1968**, 33, 4090; Arndt, F., Org. Syn. Coll. Vol. 2, 461.
11. MMX calculations suggested a difference of 6 Kcal/mol for the two epimers. Further evidence came through its $NaBH_4$ reduction to two isomeric alcohols and their Eu induced ^1H NMR shift studies.
12. Muzart, J., Tetrahedron Lett., **1987**, 28, 4665.

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