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An enantiospecific approach to (+)-thaps-8(11)-en-3-ol†

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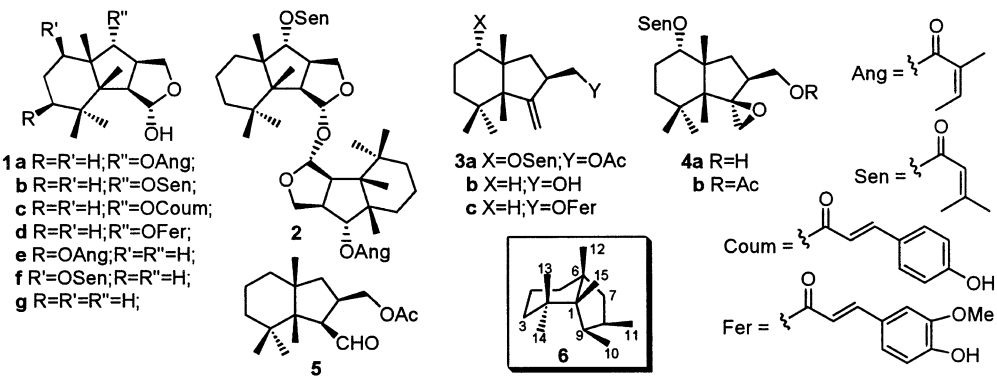
Abstract—An enantiospecific synthesis of a thapsane containing an oxygen substituent at the C-3 position is accomplished starting from (*R*)-carvone. A Claisen rearrangement and an intramolecular diazoketone cyclopropanation reaction were employed for the stereo- and regiospecific generation of the three contiguous quaternary carbon atoms present in the thapsanes. © 2002 Published by Elsevier Science Ltd.

Thapsanes **1**–**5** are a small group of sesquiterpenes isolated from the Mediterranean umbelliferous plant *Thapsia villosa*.[1] A characteristic of the structure of thapsanes is the presence of a *cis*-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane (**6**) carbon framework incorporating three contiguous quaternary carbon atoms, which poses a significant synthetic challenge.[1] So far there is only one report[2] on a synthesis of thapsanes in optically active form. Herein, we report an enantiospecific approach, starting from (*R*)-carvone **7**, to a thapsane containing an oxygen functionality at the C-3 carbon.



A retrosynthetic analysis on the basis of an intramolecular diazoketone cyclopropanation and a Claisen rearrangement is depicted in Scheme 1. It was anticipated that intramolecular cyclopropanation of the diazoketone derived from the acid **8** could generate the tricyclic ketone **9**, which would be further elaborated into thapsane **10**. Identifying the isopropenyl group as a masked hydroxy group, (*R*)-carvone **7** was chosen as the chiral precursor for the generation of the acid **8**.

The synthetic sequence started from (*S*)-3,4,4-trimethylcarvone **11**, obtained[3] from (*R*)-carvone **7** via kinetic alkylation followed by an alkylative 1,3-enone transposition (Scheme 2). Thus, reduction of trimethylcarvone **11** with lithium aluminium hydride (LAH) furnished the *syn* allyl alcohol **12**, mp 89–91°C, $[\alpha]_D^{25}$ +59.2 (*c* 1.3, $CHCl_3$), in a highly stereoselective manner.[4] Johnson's orthoester Claisen rearrangement[5] of the allyl alcohol **12** at 180°C with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube, followed by hydrolysis of the resulting ester **13a** furnished the γ,δ-unsaturated acid **13b**, mp 83–85°C (sublimed), $[\alpha]_D^{23}$ −20 (*c* 1, $CHCl_3$). The acid **13b** was converted into the diazo ketone **14** via the corresponding acid chloride. Regio- and stereospecific intramolecular cyclopropanation[6] using copper and anhydrous copper sulfate transformed

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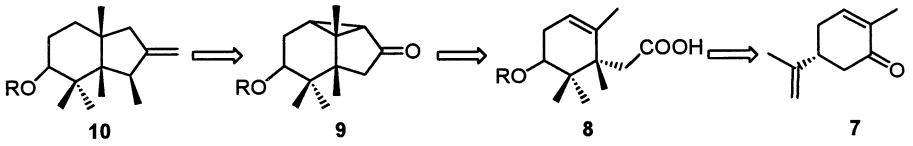
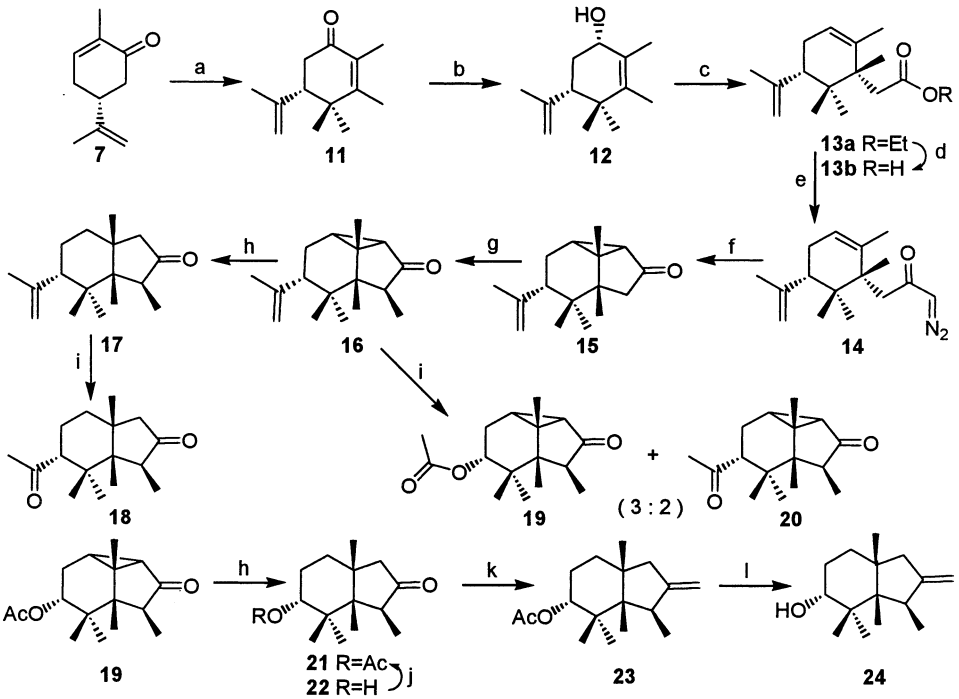


Scheme 1.



Scheme 2. *Reagents, conditions and yields*: (a) Ref. 3; (b) LAH, Et_2O, −70°C, 3 h, 90%; (c) $MeC(OEt)_3$, EtCOOH, sealed tube, 180°C, 72 h, 35%; (d) 20% KOH in MeOH, reflux, 24 h, 88%; (e) i. $(COCl)_2$, C_6H_6, rt, 3 h, ii. CH_2N_2, Et_2O, 0°C–rt, 3 h; (f) Cu, anhydrous $CuSO_4$, cyclohexane, *W*-lamp, reflux, 5 h; 56% (from acid **13b**); (g) KH, THF, 0°C, 2 h, MeI, rt, 22 h, 75%; (h) Li, liq. NH_3, THF, 10 min, 75% (for **17**), 64% (for **21**); (i) O_3/O_2, CH_2Cl_2–MeOH (3:1), −70°C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 6 h, 50% (for **18**), 64% (for **19**+**20**); (j) Ac_2O, py, DMAP, rt, 24 h, 84%; (k) $Ph_3P^+CH_3\ I^-$, $K^+\ {}^tAmO^-$, C_6H_6, rt, 3 h, 72%; (l) LAH, Et_2O, 0°C–rt, 3 h, 90%.

the diazo ketone **14** into the tricyclic ketone **15**. Regio- and stereoselective alkylation of the tricyclic ketone[‡] **15**

[‡] All the compounds exhibited spectral data consistent with their structures. Yields refer to isolated and chromatographically pure compounds. Spectral data for the tricyclic ketone **15**: Mp 94–95°C. $[\alpha]_D^{25}$ +145 (*c* 1, $CHCl_3$). IR (thin film): ν_{max}/cm^{-1} 1708, 1635, 897. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.85 (1H, s), 4.70 (1H, s), 2.25 (1H, dd, *J* 13.8 and 4.8 Hz), 2.21 (1H, d, *J* 19.2 Hz), 2.02–1.90 (1H, m), 1.90 (1H, d, *J* 19.2 Hz), 1.74 (3H, s), 1.80–1.65 (1H, m), 1.61 (1H, d, *J* 9.3 Hz), 1.37 (1H, dt, *J* 14.2 and 6.3 Hz), 1.32 (3H, s), 1.22 (3H, s), 1.10 (3H, s), 0.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 211.0 (C), 146.6 (C), 113.7 (CH_2), 53.8 (CH), 52.8 (CH_2), 43.4 (C), 42.6 (CH), 38.1 (C), 35.1 (C), 29.6 (CH), 29.1 (CH_3), 24.2 (CH_2), 23.5 (CH_3), 22.9 (CH_3), 22.7 (CH_3), 20.4 (CH_3). For the compound **16**: $[\alpha]_D^{24}$ +90 (*c* 1, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1716, 1636, 892. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.85 (1H, s), 4.71 (1H, s), 2.28 (1H, dd, *J* 14.0 and 5.0 Hz), 2.03 (1H, q, *J* 7.3 Hz), 2.01–1.90 (1H, m), 1.82–1.64 (1H, m), 1.72 (3H, s), 1.58 (1H, d, *J* 9.0 Hz), 1.46 (1H, dt, *J* 14.4 and 6.0 Hz), 1.29 (3H, s), 1.08 (3H, s), 1.06 (3H, s), 0.99 (3H, d, *J* 7.3 Hz), 0.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 213.3 (C), 146.6 (C), 113.5 (CH_2), 54.0 (CH), 51.1 (CH), 45.6 (C), 41.3 (CH), 39.2 (C), 33.9 (C), 29.5 (CH), 29.0 (CH_3), 24.1 (CH_2), 22.5 (2 C, CH_3), 21.1 (CH_3), 17.1 (CH_3), 12.6 (CH_3). For the keto-acetate **19**: $[\alpha]_D^{24}$ −24.6 (*c* 1.14, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1738, 1715. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.64 (1H, dd, *J* 7.2 and 3.0 Hz), 2.60 (1H, q, *J* 7.3 Hz), 2.53 (1H, td, *J* 16.5 and 7.4 Hz), 1.97 (3H, s), 1.76 (1H, d, *J* 16.5 Hz), 1.65 (1H, d, *J* 10.2 Hz), 1.60–1.40 (1H, m), 1.29 (3H, s), 1.13 (3H, s), 1.09 (3H, d, *J* 7.0 Hz), 1.08 (3H, s), 0.87 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 215.8 (C), 170.0 (C), 76.0 (CH), 53.1 (CH), 43.5 (C), 40.0 (CH), 39.1 (C), 33.8 (C), 28.1 (CH), 24.6 (CH_3), 24.4 (CH_2), 22.1 (CH_3), 21.8 (CH_3), 21.4 (CH_3), 15.9 (CH_3), 15.7 (CH_3). For the keto−acetate **21**: Mp 100–102°C. $[\alpha]_D^{24}$ +16.7 (*c* 1.56, $CHCl_3$). IR (thin film): ν_{max}/cm^{-1} 1726. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.78 (1H, br s), 3.17 (1H, q, *J* 6.7 Hz) 2.24 (1H, d, *J* 18.6 Hz), 2.05 (3H, s), 1.98 (1H, d, *J* 18.6 Hz), 1.95 (1H, td, *J* 14.4 and 3.0 Hz), 1.78 (1H, dt, *J* 13.8 and 3.0 Hz), 1.64 (1H, qd, *J* 14.4 and 3.0 Hz), 1.26 (3H, s), 1.09 (3H, d, *J* 6.7 Hz), 1.09 (3H, s), 1.06–1.02 (1H, m), 0.96 (3H, s), 0.89 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 219.8 (C), 169.6 (C), 79.2 (CH), 53.4 (CH_2), 50.7 (CH), 47.7 (C), 39.9 (C), 39.5 (C), 31.4 (CH_2), 26.2 (CH_3), 24.6 (CH_3), 23.3 (CH_3), 23.0 (CH_2), 21.4 (CH_3), 14.5 (CH_3), 13.0 (CH_3). For the thapsenyl acetate **23**: $[\alpha]_D^{21}$ −8.1 (*c* 1.36, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1740, 1651, 874. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.81 (1H, s), 4.77 (1H, s), 4.70 (1H, s), 3.40–3.25 (1H, m), 2.43 (1H, qd, *J* 16.0 and 3.0 Hz), 2.05 (3H, s), 1.96 (1H, d, *J* 16.0 Hz), 1.95–1.75 (3H, m), 1.65–1.54 (1H, m), 1.09 (3H, s), 1.07 (3H, d, *J* 6.9 Hz), 1.0 (3H, s), 0.94 (3H, s), 0.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 170.0 (C), 156.4 (C), 105.7 (CH_2), 79.8 (CH), 49.2 (C), 49.1 (CH_2), 43.5 (CH), 42.3 (C), 39.9 (C), 30.4 (CH_2), 26.0 (CH_3), 24.7 (CH_3), 23.3 (CH_3), 23.2 (CH_2), 21.5 (CH_3), 17.9 (CH_3), 14.0 (CH_3). For thapsenol **24**: Mp 105–107°C. $[\alpha]_D^{25}$ +16.3 (*c* 0.8, $CHCl_3$). IR (thin film): ν_{max}/cm^{-1} 3478, 1646, 874. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.78 (1H, s), 4.73 (1H, s), 3.60–3.45 (2 H, m), 2.42 (1H, qd, *J* 16.1 and 2.9 Hz), 2.05–1.85 (3H, m), 1.60–1.35 (3H, m), 1.08 (3H, s), 1.06 (3H, s), 1.06 (3H, d, *J* 6.9 Hz), 0.90 (3H, s), 0.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.8 (C), 105.4 (CH_2), 78.4 (CH), 49.4 (CH_2), 49.2 (C), 43.6 (CH), 42.5 (C), 40.2 (C), 29.8 (CH_2), 26.2 (2 C, CH_3 and CH_2), 25.0 (CH_3), 23.4 (CH_3), 18.1 (CH_3), 14.2 (CH_3).

with potassium hydride and methyl iodide furnished compound‡ **16**, which on regioselective cyclopropane ring cleavage with lithium in liquid ammonia[7] furnished the bicyclic ketone **17**. The stereochemistry of the secondary methyl group in **16** was assigned on the basis of the preferential approach of the electrophile from the sterically less crowded *exo* side of the molecule. For the degradation of the isopropenyl group, ozonolysis and Criegee rearrangement[8] was contemplated. However, ozonolysis of the bicyclic ketone in methanol–methylene chloride followed by treatment with acetic anhydride, triethylamine and 4-*N*,*N*-dimethylaminopyridine (DMAP) in refluxing benzene furnished only the normal ozonolysis product **18**. Hence, degradation of the isopropenyl group in the tricyclic ketone **16** was explored. Thus, ozonolysis in methanol–methylene chloride followed by Criegee rearrangement of the resultant methoxyhydroperoxide with acetic anhydride, triethylamine and DMAP in refluxing benzene transformed compound **16** into a 3:2 mixture of the ketoacetate‡ **19** and the dione **20**, mp 135°C (sublimed), $[\alpha]_D^{25}$ −17.5 (*c* 1.95, $CHCl_3$), which were separated by column chromatography on silica gel. Lithium in liquid ammonia-mediated regioselective cyclopropane ring cleavage[7] converted the ketoacetate **19** into the bicyclic ketoacetate **21** along with varying amounts (10–15%) of the hydroxyketone **22**. Finally, Wittig olefination of the ketoacetate **21** using methylenetriphenylphosphorane furnished thaps-8(11)-en-3-yl acetate‡ **23**, which on reaction with LAH furnished thaps-8(11)-en-3-ol‡ **24**.

In conclusion, we have developed an enantiospecific approach to a thapsane containing an oxygen functionality at the C-3 position. A regiospecific Claisen rearrangement and an intramolecular diazoketone cyclopropanation reaction were employed for the stereospecific generation of three contiguous quaternary carbon atoms. Currently, we are investigating the extension of this methodology to natural thapsanes.

Acknowledgements

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