First Total Synthesis of a Natural Thapsane

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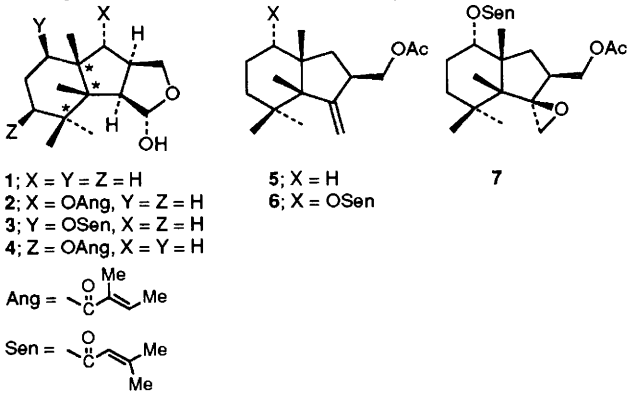
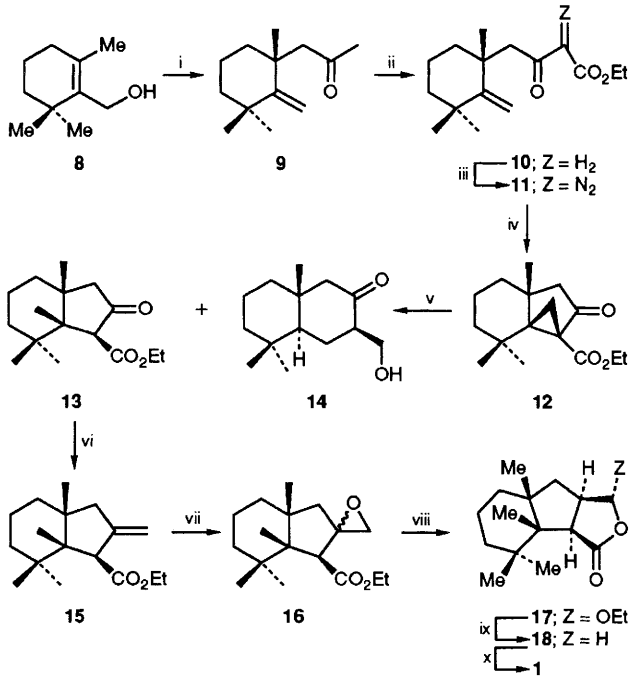
A stereospecific first total synthesis of a natural thapsane **1**, from the readily available cyclogeraniol **8**, is described.

Recently, a series of thapsanes, both hemiacetalic *e.g.* **1–4**, and open form *e.g.* **5–7**, have been isolated from the Mediterranean umbelliferous plant *Thapsia villosa* var *minor*.[1] A characteristic of the structure of this new class of hemiacetalic sesquiterpenes is the presence of the unique *cis*, *anti*, *cis*-3b,4,4,7a-tetramethyldecahydroindeno[1,2-*c*]-furan moiety, incorporating three contiguous (*) quaternary carbons posing a significant synthetic challenge. Herein, we describe the first total synthesis[2] of a natural thapsane **1**, starting from the readily available[2] cyclogeraniol **8**, using a combination of Claisen rearrangement and a stereospecific intramolecular diazoketone cyclopropanation as key reactions, incidentally without using any protection–deprotection steps.

Retrosynthetic analysis of the thapsane **1** molecule readily identified the γ,δ-unsaturated ester **15**, and the cyclopropyl ester **12** as the two key intermediates leading to **1** from cyclogeraniol. We, therefore adopted the **8** → **12** → **15** → **18** → **1** approach to thapsane (Scheme 1). Claisen rearrangement[3] of cyclogeraniol **8** with 2-methoxypropene in the presence of a catalytic amount of propionic acid furnished the ketone **9**, in 65% yield. Generation of the kinetic enolate of **9** with $LiN(Me_3Si)_2$ (3 equiv.) and quenching with ethyl chloroformate gave the β-ketoester **10**, in 80% yield. Transformation of **10** into the key diazo compound **11**, (ν_{max}/cm^{-1} 2135, 1720, 1660, 905), was conveniently achieved *via* the diazotransfer[4] with tosyl azide in the presence of triethylamine. Decomposition of **11** with a catalytic amount of rhodium acetate in benzene,[5] stereospecifically furnished the cyclopropyl ester **12**, m.p. 68 °C, in 65% yield.† Cleavage of the cyclopropane ring in **12** using lithium in liquid ammonia reduction conditions, produced a 1 : 1 mixture of the β-ketoester **13** and the decalin derivative[6] **14**, in 65% yield. The structures of **13** and **14** were delineated from their spectral data and the β-stereochemistry for the CO_2Et group in **13** was assigned based on thermodynamic considerations.[2] Formation of the two products **13** and **14** can be rationalised as follows; transfer of an electron to the carbonyl group of either ketone or of ester, followed by the cleavage of the respective cyclopropyl bond which has maximum overlap with the π-orbital of the particular carbonyl system.[7] The β-ketoester **13** was further elaborated, and the final carbon required was introduced *via* the Wittig alkenation. Thus, reaction of **13** with a large excess of Wittig ylide [$Ph_3P^+Me\ Br^-$, Am^tOK (Am^t = *tert*-pentyl)] in refluxing benzene furnished the eneester **15**, in 78% yield† (70% conversion). Attempts to hydroborate the *exo* methylene in **15** to get the lactone **18** directly were unsuccessful. Epoxidation of the eneester **15** with magnesium monoperphthalate gave a 1 : 1 diastereoisomeric mixture of the epoxides **16**. Treatment of the epoxide mixture **16** with a catalytic amount of $BF_3{\cdot}OEt_2$ furnished the hemiacetal **17**, m.p. 98–100 °C,† instead of the expected ester aldehyde. The hemiacetal **17** was converted to the lactone **18**, the oxidation product of thapsane **1**,[1d] using triethylsilane. Thus, treatment of **17** with triethylsilane in refluxing trifluoroacetic acid[8] furnished the lactone **18**, m.p. 120–23 °C (lit.[1d] 123–25 °C), in 80% yield, which exhibited ^1H and ^{13}C NMR spectra identical





Scheme 1 *Reagents and conditions*: i, $CH_2{=}C(OMe)Me$ (5 equiv.), $EtCO_2H$ (cat.), toluene, 160 °C, 48 h, 65%; ii, (a) $LiN(Me_3Si)_2$ (3 equiv.), tetrahydrofuran (THF), −78 °C; (b) $ClCO_2Et$, −78 °C → room temp., 80%; iii, TsN_3, Et_3N, MeCN, room temp., 12 h, 83%; iv, $Rh(OAc)_2$ (cat.), C_6H_6, room temp., 24 h, 65%; v, (a) Li, liq. NH_3, THF, −33 °C, 10 min; (b) NH_4Cl, 65% (**13**:**14**; 1:1); vi, $Ph_3P^+MeBr^-$ (5 equiv.), 1 mol dm^{-3} Am^tOK in Am^tOH (5 equiv.), C_6H_6, reflux, 12 h, 78% (70% conversion); vii, magnesium monoperphthalate, EtOH, 24 h, room temp., 69%; viii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temp., 2 h, 49%; ix, Et_3SiH, CF_3CO_2H, reflux, 5 h, 80%; x, DIBAH (1.1 equiv.), toluene, −78 °C, 1.5 h, 82%

† *Selected spectral data* for **12**: ν_{max}/cm^{-1} 1745, 1120, 1070. δ_H (270 MHz, $CDCl_3$): 0.65 (3 H, s), 1.17 (3 H, s), 1.22 (3 H, s), 1.3 (3 H, t, *J* 7.2 Hz), 1.3–1.7 (7 H, m), 1.87 (1 H, d, *J* 5.7 Hz), 1.79 and 2.13 (2 H, AB q, *J* 18 Hz), 4.19 (2 H, q, *J* 7.2 Hz). δ_C (22.5 MHz, $CDCl_3$): 207 (s), 167.7 (s), 60.6 (t), 54.1 (s), 49.3 (t), 49 (s), 38.9 (t), 38.6 (t), 38.1 (s), 33 (s), 27.6 (q), 26.8 (q), 22.5 (q), 18.1 (t), 17.7 (t), 13.6 (q). For **15**: ν_{max}/cm^{-1} 1746, 1040, 880. δ_H (200 MHz, $CDCl_3$): 0.83 (3 H, s), 0.98 (3 H, s), 1.1 (6 H, s), 1.28 (3 H, t, *J* 7.2 Hz), 1.15–1.7 (6 H, m), 1.97 (1 H, d, *J* 16.3 Hz), 2.53 (1 H, qd, *J* 16.3 and 2.9 Hz), 3.7 (1 H, q, *J* 2.7 Hz), 4.13 (2 H, m), 4.81 (1 H, q, *J* 2.5 Hz), 4.9 (1 H, q, *J* 2.5 Hz). δ_C (22.5 MHz, $CDCl_3$): 174.2 (s), 149.3 (s), 107.9 (t), 59.9 (t), 54.7 (d), 52.5 (s), 48.7 (t), 43 (s), 37.6 (t), 36.3 (t), 36.1 (s), 28.6 (q), 25 (q), 22.6 (q), 18.8 (t), 14.3 (q), 13.9 (q). For **17**: ν_{max}/cm^{-1} 1776, 1122, 960. δ_H (400 MHz, $CDCl_3$): 0.92 (3 H, s), 0.97 (3 H, s), 1.08 (6 H, s), 1.2 (3 H, t, *J* 7.1 Hz), 1.1–1.6 (6 H, m), 1.7 (2 H, dd, *J* 10 and 1.7 Hz), 2.85 (1 H, dq, *J* 11 and 2 Hz), 3.38 (1 H, d, *J* 11 Hz), 3.5 and 3.9 (2 H, q of AB q, *J* 9 and 7 Hz), 5.13 (1 H, d, *J* 2 Hz). δ_C (22.5 MHz, $CDCl_3$): 177 (s), 107.9 (d), 64.9 (t), 52.1 (s), 51.4 (d), 47 (s), 45.5 (t), 44.4 (d), 38.6 (t), 36.4 (t), 35.9 (s), 30.4 (q), 24.6 (q), 22.8 (q), 18.6 (t), 15.1 (2 C, q).

with those derived from the natural product.[1d] Finally, the lactone **18** on reduction with diisobutylaluminium hydride (DIBAH) generated the thapsane **1**, m.p. 81–82 °C (lit.[1d] 85 °C), in 82% yield.

In conclusion, we have described here the first total synthesis of a natural thapsane, and currently we are investigating the extension of this methodology for other thapsanes.

We thank Professor S. B. Christensen for providing the spectral data for the lactone **18** and the thapsane **1**. We are grateful to the CSIR, New Delhi for the financial assistance. The generous gift of β-ionone by M/s Kelkar & Co is gratefully acknowledged.

Received, 2nd August 1991; Com. 1/04036G

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