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The first enantiospecific synthesis of (+)-10,11-epoxythapsan-10-ol: revision of the absolute stereochemistry of thapsanes†

A. Srikrishna* and K. Anebouselvy

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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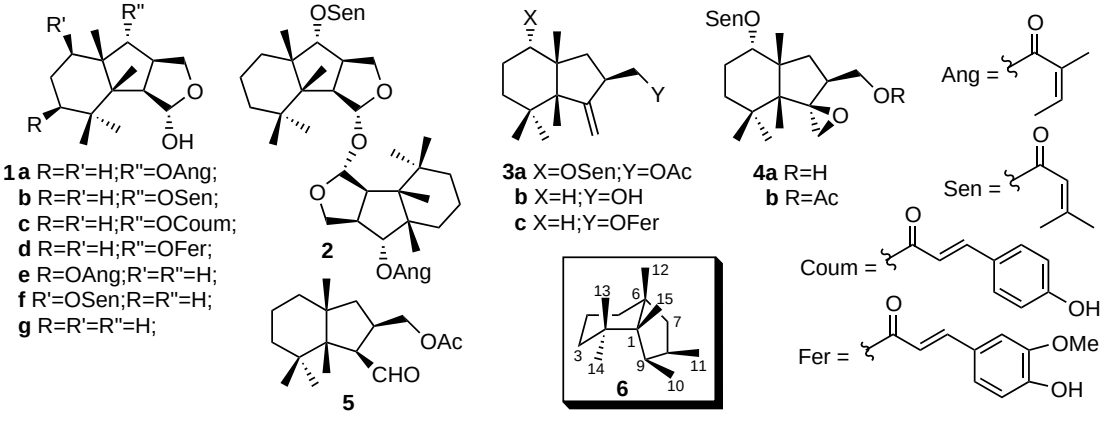
Abstract—The first enantiospecific synthesis of (+)-*cis*,*anti*,*cis*-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-3-ol (+)-**1g**, an enantiomer of natural thapsane isolated from *Thapsia villosa* var *minor*, is accomplished starting from (*R*)-carvone, which revises the absolute stereochemistry of natural thapsanes.

Rasmussen and co-workers reported[1] the isolation of the sesquiterpene **1a** from the ethanolic extract of the roots of the Mediterranean umbelliferous plant, *Thapsia villosa* L. Simultaneously, Grande and co-workers reported[2] the isolation of the corresponding senicioate ester **1b** from the benzene extract of the roots of *T. villosa* var *minor*, along with five other hemiacetalic **1c–f**, **2**, and four nonacetalic **3a**, **4a**,**b**, **5** minor components, having the same carbon framework. The trivial name 'thapsane' was suggested for the bicyclic carbon framework *cis*-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane **6** containing the three contiguous quaternary carbon atoms which are present in these sesquiterpenes. Later Christensen and co-workers reported[3] the isolation of three more thapsanes, two nonacetalic **3b**,**c** and one hemiacetalic **1g**, from *T. villosa* var *minor*. The structures of the thapsanes were established from their spectroscopic data in conjunction with chemical transformations, and were further supported by the single crystal X-ray analysis of **1a**. Rasmussen et al.[1] have assigned the absolute stereochemistry of (−)-**1a** as 1*R*,6*R*,8*R*,9*R*,10*S* by employing Horeau's empirical method for secondary alcohols. Grande and co-workers have also assigned[2] the same configuration for all the thapsanes, on the basis of the CD curves of the ketones derived from thapsanes **1e** and **1f**. A characteristic of the structure of the hemiacetalic thapsanes is the presence of a *cis*,*anti*,*cis*-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecane framework containing three contiguous quaternary carbon atoms, which poses a significant synthetic challenge. Earlier we have reported[4a] the synthesis of the racemic thapsane (±)-**1g**. So far there is no report on the synthesis of any natural thapsane in an optically active form, which would confirm the absolute stereochemistry.[5] Herein, we report the first enantiospecific synthesis of (+)-**1g**, starting from (*R*)-carvone **7**, which establishes that the absolute configuration of thapsanes is opposite to that assigned[1,2] earlier.



1a R=R'=H;R"=OAng;
b R=R'=H;R"=OSen;
c R=R'=H;R"=OCoum;
d R=R'=H;R"=OFer;
e R=OAng;R'=R"=H;
f R'=OSen;R=R"=H;
g R=R'=R"=H;

2

5

3a X=OSen;Y=OAc
b X=H;Y=OH
c X=H;Y=OFer

6

4a R=H
b R=Ac

* Corresponding author. Fax: 91-80-3600683; 3600529; e-mail: ask@orgchem.iisc.ernet.in

† Chiral synthons from carvone, Part 55. For part 54, see reference 5b.

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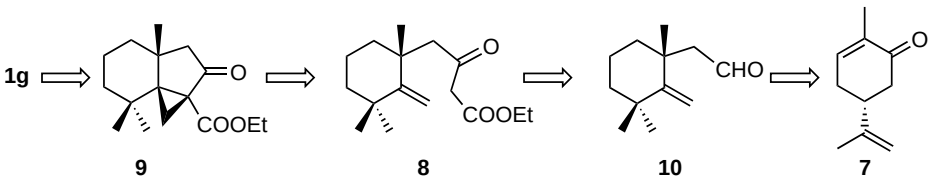
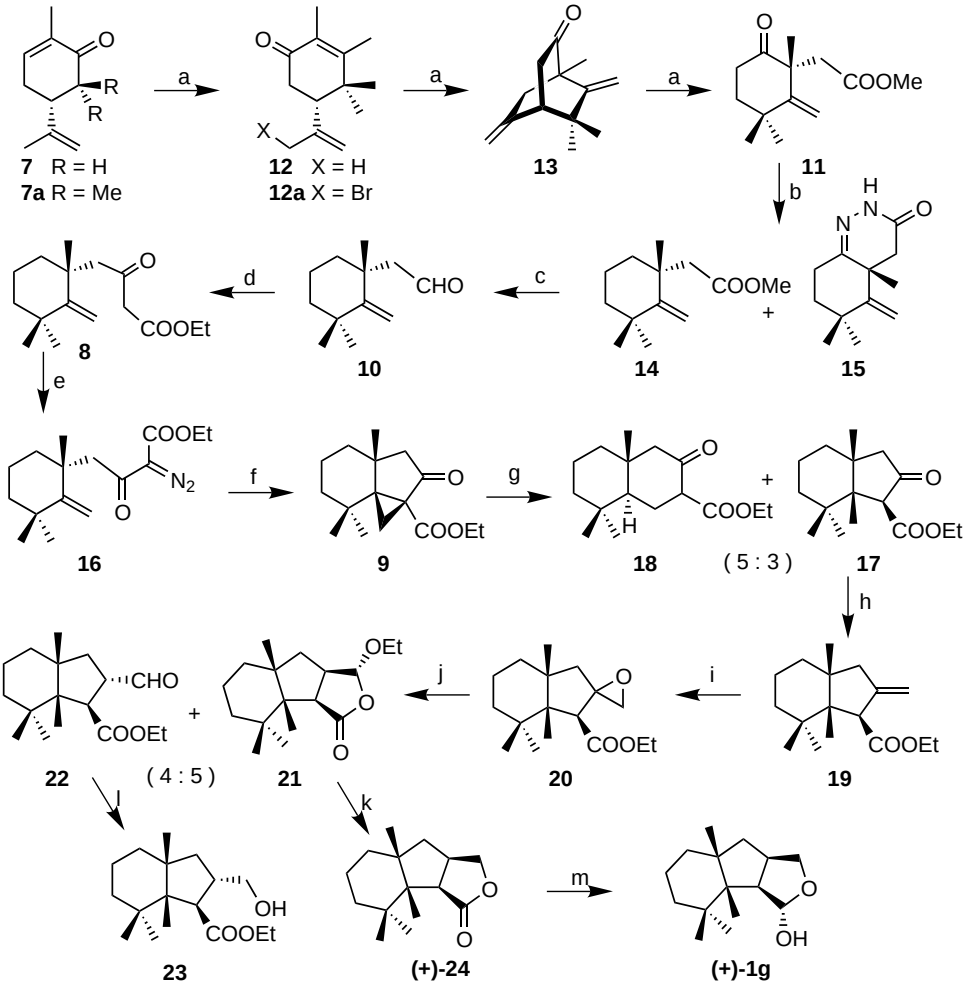
For the enantiospecific synthesis of thapsane **1g**, we have conceived a combination of our earlier approach towards racemic thapsane[4a] **1g** and the recently developed[5a] enantiospecific synthesis of a thapsenol. It was anticipated that intramolecular cyclopropanation of the diazoketone derived from the β-ketoester **8** could generate the tricyclic ketone **9**, which could be further elaborated into thapsane **1g**. It was contemplated that the aldehyde **10**, which could be obtained from (*R*)-carvone **7** in optically active form, would serve as an ideal precursor for the generation of the β-ketoester **8** (Scheme 1).

The synthetic sequence starting from (*R*)-carvone **7** is depicted in Scheme 2. To begin with, (*R*)-carvone **7** was converted into the ketoester **11**, via trimethylcarvone **12** and bicyclo[2.2.2]octanone **13**, employing a regio-, stereo- and enantiospecific translocation of the isopropenyl side chain of trimethylcarvone from the C-5 carbon to the C-2 carbon (as an acetate side chain) strategy as described earlier.[5a] Wolff–Kishner reduction of the ketoester **11** with hydrazine hydrate and potassium hydroxide in digol followed by esterification of the resultant acid with diazomethane furnished the ester **14**, $[\alpha]_D^{26}$ −3.7 (*c* 3, $CHCl_3$), in 53% yield, along with a



Scheme 1.



Scheme 2. *Reagents, conditions and yields*: (a) Ref. 5a; (b) i. $N_2H_4{\cdot}H_2O$, KOH, digol, 180°C, 12 h; ii. CH_2N_2, Et_2O, 0°C, 10 min; 75%, **14**:**15** 5:2; (c) i. LAH, Et_2O, 0°C–rt, 2.5 h, 91%; ii. PCC, silica gel, CH_2Cl_2, rt, 1 h, 83%; (d) N_2CHCO_2Et, $SnCl_2{\cdot}2H_2O$, CH_2Cl_2, rt, 6 h, 88%; (e) *p*-TsN_3, NEt_3, CH_3CN, rt, 12 h, 89%; (f) $Rh_2(OAc)_4$, C_6H_6, rt, 20 h, 69%; (g) Li, liq. NH_3, THF, −33°C, 5 min, 86%; (h) $Ph_3P^+CH_3\ Br^-$, $K^+\ {}^tAmO^-$, C_6H_6, reflux, 12 h, 98%; (i) MMPPA, EtOH, rt, 36 h, 83%; (j) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 2 h, 70%; (k) Et_3SiH, CF_3COOH, reflux, 5 h, 74%; (l) $NaBH_4$, MeOH, 0°C, 0.5 h, 91%; (m) DIBAL-H, hexane, −78°C, 75 min, 87%.

varying amount of the hexahydrocinnoline **15**, mp 119–121°C, $[\alpha]_D^{23}$ −85.5 (*c* 2, $CHCl_3$). Lithium aluminium hydride (LAH) reduction followed by PCC oxidation of the resultant alcohol transformed the ester **14** into the key intermediate of the sequence, aldehyde **10**, $[\alpha]_D^{23}$ +3.8 (*c* 4, $CHCl_3$). Stannous chloride catalysed reaction[6] of the aldehyde **10** with ethyl diazoacetate furnished the β-ketoester **8**, $[\alpha]_D^{25}$ −10 (*c* 5.2, $CHCl_3$), in 88% yield. A diazo transfer reaction with tosyl azide and triethylamine converted the ketoester **8** into the α-diazo-β-ketoester **16** in 89% yield. A rhodium acetate catalysed stereospecific intramolecular cyclopropanation[7] reaction of the diazo compound **16** resulted in the formation of the tricyclic compound **9**,† in 69% yield. Reductive cleavage of the cyclopropane ring in **9** employing lithium in liquid ammonia furnished a 3:5 mixture of the hydrindanone† **17** and the decalinone **18**, $[\alpha]_D^{24}$ −52 (*c* 2.5, $CHCl_3$), in 86% yield, via electron transfer to the ketone and ester carbonyl groups,[8] respectively. A Wittig reaction of the ketoester **17** with methyltriphenylphosphonium bromide and potassium *tert*-amylate in refluxing benzene generated the ester† **19** in 98% yield. Epoxidation of the exomethylene in **19** with magnesium monoperoxyphthalate (MMPPA) in ethanol generated a ≈1:1 epimeric mixture of the epoxide **20** in 83% yield. Treatment of the epimeric mixture of the epoxide **20** with a catalytic amount of boron trifluoride diethyl etherate in methylene chloride furnished a 5:4 mixture of the ethoxylactone† **21** and the aldehyde-ester **22**, $[\alpha]_D^{25}$ +8.6 (*c* 1.4, $CHCl_3$), in 70% yield, which were separated by silica gel column chromatography. Formation of the ethoxylactone **21** could be rationalised via the boron trifluoride diethyl etherate catalysed rearrangement of the epoxide in **20** followed by intramolecular transacetalisation of the *cis*-isomer of the resultant ester aldehyde. Reduction of the aldehyde group in **22** with sodium borohydride in methanol furnished the hydroxy-ester **23** confirming the *trans*-relationship of the ester and aldehyde groups in **22**. Ionic hydrogenation of the ethoxylactone **21** using a combination of trifluoroacetic acid and triethylsilane furnished the lactone **24**, mp 120–123°C (lit.[2b] 123–125°C), $[\alpha]_D^{25}$ +43.3 (*c* 1, $CHCl_3$) {lit.[2b] −41 (*c* 1.4, $CHCl_3$)}, a degradation product of a number of thapsanes.[2] Finally, reduction of the lactone **24** with diisobutylaluminium hydride furnished the thapsane **1g**, mp 85–87°C (lit.[3] 85.5–87°C), $[\alpha]_D^{25}$ +40 (*c* 0.5, $CHCl_3$) {lit.[3] −47 (*c* 0.16, $CHCl_3$)}. The lactone **24** and the thapsane **1g** exhibited ^1H and ^{13}C NMR spectra identical to those of the compounds derived from Nature, but exhibited the opposite optical rotation, establishing the configuration of the natural thapsanes to be opposite from that originally assigned.[1,2]

In conclusion, we have developed the first enantiospecific approach to an *ent*-thapsane, which unambiguously established the absolute configuration of the natural thapsanes as 1*S*,6*S*,8*S*,9*S*, which is the opposite to that assigned earlier by the research groups of Rasmussen and Grande. Currently, we are investigating the extension of this methodology to other natural thapsanes.

Acknowledgements

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† All the compounds exhibited spectroscopic data consistent with their structures. Yields refer to isolated and chromatographically pure compounds. Spectral data for the tricyclic compound **9**: mp: 68°C. $[\alpha]_D^{24}$ −37.5 (*c* 1.2, $CHCl_3$). IR (thin film): ν_{max} 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.19 (2H, q, *J*=7.5 Hz), 2.08 (1H, d, *J*=17.5 Hz), 1.82 (1H, d, *J*=5.7 Hz), 1.75 (1H, d, *J*=17.5 Hz), 1.80–1.35 (7H, m), 1.31 (3H, t, *J*=7.2 Hz), 1.22 (3H, s), 1.17 (3H, s), 0.64 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 206.8 (C), 168.0 (C), 61.2 (CH_2), 54.4 (C), 49.9 (CH_2), 49.4 (C), 39.5 (CH_2), 39.2 (CH_2), 38.7 (C), 33.6 (C), 28.3 (CH_3), 27.5 (CH_3), 23.2 (CH_3), 18.7 (CH_2), 18.3 (CH_2), 14.2 (CH_3). For the ketoester **17**: $[\alpha]_D^{24}$ +70.0 (*c* 1.4, $CHCl_3$). IR (thin film): ν_{max} 1753, 1726 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.15 (2H, q of AB q, *J*=10.5 and 7.0 Hz), 3.70 (1H, s), 2.40 and 1.97 (2H, 2×d, *J*=18.5 Hz, H-9), 1.75–1.35 (6H, m), 1.27 (3H, t, *J*=7.0 Hz), 1.24 (3H, s), 1.21 (3H, s), 1.07 (3H, s), 0.86 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 210.8 (C), 169.6 (C), 61.6 (CH), 60.6 (CH_2), 53.6 (CH_2), 51.2 (C), 40.5 (C), 37.4 (CH_2), 37.2 (CH_2), 36.4 (C), 28.8 (CH_3), 25.4 (CH_3), 22.8 (CH_3), 18.6 (CH_2), 14.5 (CH_3), 14.2 (CH_3). For the ester **19**: $[\alpha]_D^{25}$ 23.6 (*c* 2.8, $CHCl_3$). IR (neat): ν_{max} 1745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.83 (1H, s), 4.75 (1H, s), 4.08 and 4.04 (2H, q of AB q, *J*=11.7 and 7.0 Hz), 3.71 (1H, m), 2.47 (1H, q of d, *J*=16.5 and 3.0 Hz), 1.91 (1H, d, *J*=16.5 Hz), 1.60–1.10 (6H, m), 1.21 (3H, t, *J*=7.0 Hz), 1.03 (6H, s), 0.92 (3H, s), 0.76 (3H, s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 174.2 (s), 149.3 (s), 107.9 (t), 59.9 (t), 54.7 (d), 52.5 (s), 48.7 (t), 43.0 (s), 37.6 (t), 36.3 (t), 36.1 (s), 28.6 (q), 25.0 (q), 22.6 (q), 18.8 (t), 14.3 (q), 13.9 (q). For the ethoxylactone **21**: mp: 98–100°C. $[\alpha]_D^{25}$ −71.7 (*c* 1.66, $CHCl_3$). IR (thin film): ν_{max} 1765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.05 (1H, s), 3.84 (1H, q of d, *J*=9.0 and 7.0 Hz), 3.50 (1H, q of d, *J*=9.0 and 7.0 Hz), 3.33 (1H, d, *J*=10.8 Hz), 2.82 (1H, q, *J*=9.9 Hz), 1.68 (2H, d, *J*=9.3 Hz), 1.65–1.10 (6H, m), 1.21 (3H, t, *J*=7.0 Hz), 1.08 (6H, s), 0.97 (3H, s), 0.91 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 176.1 (C), 107.5 (CH), 64.7 (CH_2), 52.1 (C), 51.3 (CH), 47.1 (C), 45.7 (CH_2), 44.4 (CH), 38.7 (CH_2), 36.6 (CH_2), 36.0 (C), 30.6 (CH_3), 24.8 (CH_3), 23.0 (CH_3), 18.7 (CH_2), 15.2 (CH_3), 15.0 (CH_3).

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